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A PARTICULAR VARIETY OF HEADACHE

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THE purpose of this communication is to define a clinical syndrome which is of comparatively rare occurrence and, though well recognized by many neurologists, has not so far as the writer is aware been described in any great detail. Of its cause there is little that can be said except by way of analogy and speculation. Concerning its treatment some observations will be offered which, because the pain is commonly of excruciating severity, may be of practical value.

The material available for this purpose comprises 17 cases observed in consulting practice. These have been selected from a larger number probably belonging to the same group. The reasons for discarding cases have been failure on the part of the observer to make a complete record of the essential data, or a duration of the malady too short to provide a proper perspective. The importance of the latter requirement will be apparent when the syndrome has been described. Its essential features are the occurrence of paroxysms of headache, that is to say, pain of sudden onset and transitory duration, which occur in bouts lasting as a rule for several weeks with long intervals of perfect freedom. In the paroxysm the pain is felt mainly in the supra-orbital region or in and behind the eye, though it may spread beyond this region. It is, however, strictly unilateral. It is of agonizing severity, but very rarely lasts longer than two hours and often less. During a bout there is usually at least one paroxysm in each twenty-four hours; there may be more. In the intervals between paroxysms there is complete relief. The bout having ended, there is no further complaint of headache until the occurrence of the next bout after an interval of freedom, which is rarely less than six months and may be several years. No local cause for the pain is to be discovered in the shape of disease of the eyes, nose, nasal sinuses, ears, scalp or skull, or the sensory nerves supplying the region where the pain is felt.

Following this general description of the syndrome a more detailed

account of its features will be given from the analysis of the writer's material.

The duration of bouts.—The general rule was that from the first the bouts had lasted a week or more, and in 9 out of 16 cases in which the minimum duration was recorded it was two or more weeks. At the other extreme the duration of a bout never exceeded ten weeks, with one exception. The longer bouts had always occurred late in the story. The exceptional case, *Case* 5, which will be described fully under the heading of treatment, was one in which there was a story of bouts lasting five or six weeks recurring at intervals of six months for seventeen years, followed, after the usual interval, by a period of fourteen months, with two intermissions of less than a week, during which paroxysms occurred at least once in the twenty-four hours and were continuing to occur whenever ergotamine tartrate was omitted when the patient last reported.

In 5 cases there was a history in the early stages of the malady of isolated paroxysms, or paroxysms recurring for a few days only. The following case illustrates this mode of development, together with another uncommon feature, a frequency of less than one paroxysm in the twenty-four hours during a prolonged bout.

Case 1.—Male, aged 39 when first seen in 1948. At the age of 35 began to have attacks of pain behind the left eye described as like pain in a tooth exposed to cold, reaching peak intensity in fifteen minutes, remaining thus for an hour or an hour and a half, then rapidly disappearing, but sometimes followed by a dull ache for an hour or two. At the height of the attack the eye would water and become bloodshot and the left side of the nose would feel blocked. The attack would usually begin between 2 a.m. and 3 a.m. and would be repeated for two or three nights in succession. After an interval of six or eight weeks the experience would be repeated.

When seen again in November 1955, he reported that the nature of the attacks had remained unaltered, but that the series or bout had gradually become longer, lasting up to a fortnight, and the intervals between bouts had also lengthened up to six months. Then in the summer of 1952 he had a bout lasting four weeks followed by complete freedom for eighteen months. There was then a bout lasting two weeks, again followed by freedom for eighteen months, when he began a bout which had lasted for five weeks when he was seen. In this the paroxysms had occurred at irregular times, mainly during the night, but occasionally in the day. On two occasions there had been three paroxysms in the twenty-four hours. But on several occasions he had gone twenty-four hours without a paroxysm.

The *frequency of the paroxysms* during a bout has varied from one to eight in each twenty-four hours. The usual story was that from the onset of the bout there was at least one paroxysm in the twenty-four hours. In 6 cases it was never more than one. At the beginning of a bout, however, the frequency might be less than one paroxysm in the twenty-four hours, and in *Case* 1 this occasional omission continued throughout an established bout. 6 patients reported the frequency

of paroxysms in some bouts as four or more in the twenty-four hours. In all except one of these the main incidence was during the night, but as the nocturnal attacks became more frequent paroxysms might also occur during the day. In the remaining case, which will be reported fully under the heading of treatment, the paroxysms were equally frequent during the night and day.

The *time of onset of the paroxysms* was in 12 out of the 17 cases mainly nocturnal with a tendency for attacks to occur during the day only if their frequency became more than one in the twenty-four hours. The time of the nocturnal attacks varied not only with different patients but with different bouts in the same patient, but in a particular bout was often constant. This regularity of time incidence might also be observed when paroxysms occurred during the day. 8 patients had observed this as a striking feature of the malady, especially in the earlier bouts. Thus in 3 cases with a single nocturnal paroxysm the time of onset was 12.30 a.m., 3.30 a.m. and 2 a.m. respectively during repeated bouts. Another patient with recurrent bouts lasting five to six weeks observed that the time of onset would be 1 a.m. for a few nights, then 2.30 a.m. for two or three weeks, with a sudden change to 6 a.m. for the remainder of the bout. 4 patients whose paroxysms might occur at any time during the twenty-four hours stated that the time varied from one bout to another, but in any particular bout was constant. A typical story was that of *Case* 2, who had had six bouts in three years, varying in duration from three to five weeks, during which he had one paroxysm in each twenty-four hours. In the first bout, and in three others, the time was regularly 2 a.m., but in one bout the paroxysm came at 2 p.m., and in another at 9 p.m. with constant regularity.

The *duration of the paroxysm* varied from ten minutes to five hours, but in only 3 cases had it ever been longer than two hours. In these 3 cases the occurrence of a paroxysm lasting longer than two hours was exceptional. 5 patients had experienced paroxysms lasting less than half an hour. In 2 of these the duration was always short and had remained so throughout many bouts, between ten and twenty minutes in one case and fifteen to twenty minutes in the other. In 2 cases the paroxysms had been brief in the earlier bouts but subsequently became longer, and the remaining patient stated that in his earlier bouts the duration was one hour but had since shortened to fifteen minutes.

The *interval between bouts* varied from ten years in 1 case to two months in another. The longest period of freedom had been one year or more in 13 cases. The shortest interval between bouts was less than six months in only 3 cases. 3 patients experienced their bouts regularly at intervals of six months, in the spring and autumn. A patient who had had bouts at relatively short intervals might have a long period of remission without any apparent explanation, for example:

Case 3.—Male, aged 46 when first seen, at the age of 22 had a bout lasting three to four weeks, during which he was woken each night by pain in the right temple like toothache, spreading into the eye, and subsequently into the neck below the jaw. This reached maximal distribution and peak intensity in ten minutes, lasted from a half to two hours and then rapidly disappeared. The paroxysms might occur at any time of night. He would sometimes have one in the day also. It was associated with lacrimation and congestion of the right eye. For the next sixteen years he had a similar bout practically every year in September or October. He then had complete freedom for eight years until he was seen in January 1955, when he had been having one or two paroxysms every night for the past three weeks. A nightly injection of ergotamine tartrate 0·5 mg. was recommended, to be omitted on one night in the week. He had no further paroxysms so long as he took the injections, and the bout came to an end ten days later.

The site and character of the pain, and associated symptoms.—The initial site of the pain was supra-orbital in 8 cases, in or behind the eye in 7 cases. In 2 cases it began in the temple but quickly spread to the back of the eye. Radiation of the pain occurred to some extent in all cases, but in 3 instances had never spread beyond the brow and eyeball. In other cases it might extend widely into the temporal region as far back as the ear or behind it, or more frequently into the face and jaw, and occasionally into the neck. In a single bout it was always confined to one side of the head and face, but one patient who for 16 years had had bouts of right-sided pain twice a year and lasting five or six weeks then had a bout in which exactly similar paroxysms occurred on the left side instead of the right.

The pain was always described as intense from the onset, usually increasing in severity to a peak in ten to twenty minutes, remaining at this level for a further twenty minutes or so, then rapidly diminishing and ceasing somewhat abruptly. Several patients compared it with a severe toothache, and the words sharp, vicious, stabbing, throbbing and shooting were used to describe it. Many of the sufferers were unable to keep still with it. Half the patients described the eye on the affected side as bloodshot with excessive lacrimation during the attacks, and 6 stated that the nose on that side felt as if blocked.

One patient, *Case* 4, was observed during an attack. He had been first seen at the age of 45 with a seven-year history of recurrent bouts at irregular intervals of a year or more, lasting four to six weeks, and described his pain as starting above the left eye and running down through the ear to the lower jaw. It would, he said, gather momentum, reaching its climax in ten minutes, remaining at this level for twenty minutes and then rapidly declining so that the whole attack was over in forty-five minutes. His attacks had all been exactly the same. He came again after an interval of four and a half years' complete freedom, having begun another bout a month previously in which the paroxysms were at first nocturnal but then began to occur in the day also. The

attack in which he was seen had begun twenty minutes before. When at first observed he was speechless with pain, restless, pale and sweating profusely. There was lacrimation and congestion of the eyeballs, much more evident on the left, and the left ear was warmer and redder than the right. Within twenty minutes he was able to converse, replaced his dentures, which he had removed during the attack, and stated a few minutes later that his pain was now gone.

4 patients experienced nausea with their attacks, and 2 of these had occasionally vomited.

Provoking factors.—Apart from seasonal change of temperature, which was remarked upon by 3 patients, there was no apparent cause for the bouts. In particular no evidence could be obtained for the assumption that psychological factors were operative. 2 patients had obsessional tendencies with episodes of anxiety, and 1 other suffered from chronic mild anxiety, but the bouts did not coincide with, or follow, periods of psychological tension. 2 patients were certain that during a bout in which attacks were occurring in the day alcohol was likely to precipitate an attack.

Sex.—14 of the 17 patients were males.

Age of onset.—The age of onset varied from 14 to 43 with an average of 26·9 years.

Duration of illness.—The time elapsed since the onset when the patient was first seen varied from three to twenty-four years, with an average of 12·2 years.

Family history.—In 6 cases there was a family history of headaches which appeared to be of the migrainous type, and in another case a family history of asthma and hay fever.

Previous history.—In many of these patients suspicion had been directed to infection of the nasal sinuses as a cause of the attacks, and operations had been performed without benefit. There was no evidence in any case to suggest that disease or malformation of the nose or nasal sinuses had been the cause. 2 patients gave a history of injury to the relevant side of the face before the onset of the attacks. In 1 of these cases the injury had occurred five years before the onset with post-traumatic amnesia of half an hour and a broken nose. There was no evidence from history or examination of injury to the supra-orbital or infra-orbital nerves. In the other, *Case* 1, there had been a laceration above the left eyebrow requiring seven stitches, but there was no memory of any headache or numbness following this. The attacks, which were left-sided, began twenty-five years later.

In 2 cases there was a history of recurrent headache from an early age severe enough to warrant the diagnosis of migraine. In neither of these cases had there ever been any visual or sensory aura, and the headaches occurred independently of the bouts of neuralgic pain. One patient

had experienced attacks in which he saw a zigzag pattern of lights in the upper part of his left visual field lasting less than a minute, not followed by headache and occurring independently of his bouts, which were left-sided. Another patient, *Case* 1, had on three or four occasions in the fifteen years before the onset of his malady experienced dimness or loss of vision in some part of his visual field, lasting for about half an hour and followed by a generalized dull headache with nausea. On a single occasion after the onset of his neuralgic bouts he had an attack which began in the manner of a paroxysm with severe pain in and behind the left eye, shortly followed by defect of vision such that he was unable to see objects on one side of him unless he turned his head. This lasted half an hour or more and was followed by a generalized headache with nausea.

3 patients suffered from hay fever.

Treatment.—Of the method of treatment followed in the later cases of the series a brief account has previously been given by the writer (Symonds, 1951). The 2 cases then recorded have since been followed up and will here be described in greater detail. The first was that of a patient who had discovered for himself what has proved valuable for others.

Case 5.—Male, aged 48 when first seen in 1948, began at the age of 38 to have bouts of what he called neuralgia. They had recurred about once in six months and had always followed the same pattern. He would be awakened in the night by a violent shooting pain above the right eyebrow, radiating into the temporo-parietal region. This would last from half to three-quarters of an hour, ceasing as suddenly as it came. In the attack the right side of his nose felt as if blocked. Early in the bout the attack would occur regularly at 1 a.m., later shifting to 2.30 a.m. for some nights and then to 6 a.m. He had no attacks during the day. They would occur every night for five to six weeks and then cease abruptly. Some years before he was seen by the writer Dr. Riddoch had advised an injection of 0·25 mg. ergotamine tartrate (Femergin) to be given as soon as possible after the onset of the attack. He learned to give himself the injections, but found they had no effect. He then tried giving himself the injection before going to bed and found that this would prevent the expected attack. In subsequent bouts the plan he adopted when he had an attack was to start giving himself an injection each night, but to omit it on one night in the week. If he then had an attack he would continue the injections for another week and then try a night without, and so on. It was only by this means that he could discover when the bout was at an end. The duration of the bout, he had found, was unaltered by this treatment. He was advised to continue with it and was seen again seven and a half years later, reporting that the bouts had continued to occur about once in six months. He had followed the old treatment with considerable success, but found that though his nights were free he would occasionally have an attack during the day. When this occurred he would increase the nightly dose to 0·5 mg. with success. He came again in July 1955, because he had had a much more severe and protracted bout. This began in October 1954, the pain being as usual right-sided and waking him early in the night. Its distribution was wider than before, extending into the infra-orbital region and upper teeth. Its duration was as in previous bouts. He was at first without his Femergin and in the course of a few days the paroxysms became more frequent, two or even three in the night, and one or two in the day. He then

began to give himself an injection of 0·25 mg. at night and was clear of pain till 6 a.m., but would still have attacks in the day. He therefore gave himself an additional injection of 0·25 mg. on rising. On this regime he would have an occasional paroxysm either about 6 p.m. or 6 a.m. Thus he continued until March 1955, when the attacks, having diminished in frequency, ceased and he stopped the injections. A week later he began to have attacks of pain of the same character, distribution and frequency on the left side. The pain, however, was less severe. He started the injection again in a dose of 0·25 mg. at bed-time and thereafter had clear nights, but with an occasional attack in the day. This continued for two months, after which the attacks in the day ceased but he still continued to have a paroxysm in the night on the occasion of his weekly omission of the injection. He had heard something of the toxic effects of ergot and was anxious lest by continuing the injections he should come to some harm. As he appeared to be suffering no harm from the injections he was advised to continue with them. He reported on November 21, 1955, that he had continued to have a left-sided paroxysm every Saturday night after omitting the bed-time injection. A fortnight before he wrote, however, they ceased for a few days and then began again on the right side. He occasionally had one in the day. So long as he had an injection of 0·25 mg. ergotamine tartrate night and morning he remained completely free from pain. He wrote "As this present bout of attacks has now lasted a year and two months I sincerely hope it will shortly end, but I honestly believe that without the injections I should have been either a mental case or a physical wreck long before now."

Case 6.—Male, aged 37 when first seen in 1948, had had his first bout at the age of 23, beginning with the sudden onset of severe pain deep in the left eye, lasting an hour. This occurred at noon and thereafter daily usually at the same time, though it might be as early as 9 a.m. or as late as 5 p.m. The bout lasted six weeks. Two years later he had an exactly similar bout again lasting six weeks, with subsequent recurrence of bouts at intervals varying from six months to two years. In the intervals he was completely free. In the early part of 1948 he had a bout which began in a different way. During the first fortnight he had a single paroxysm every three or four days, then a daily attack at irregular times until at the end of ten weeks the bout suddenly ended. In this case there was a family history of migraine, and he himself had had intermittent headaches from the ages of 4 to 10. His case had been diagnosed as atypical trigeminal neuralgia and alcohol injection of the ganglion proposed. He was instructed in case of another bout to give himself an injection of 0·25 mg. ergotamine tartrate night and morning, omitting the bed-time dose once a week. He reported later by letter that in February 1949, the pain had returned and that after enduring it for a week he followed these instructions with complete relief until the bout ended after another two weeks. He was seen again in June 1955, having had further bouts in 1950 and 1952, which responded to treatment so that he had no pain except when he omitted the injection. These bouts lasted eight to ten weeks. He was free until April 15, 1955, when he had daily paroxysms for a week before starting his injections of 0·25 mg. at 8 a.m. and 9 p.m. With these he continued to have occasional attacks in which the pain was of such slight degree that his work was not interrupted. This continued for a week, after which with the aid of the injections he became practically free, having only an occasional threat of pain until June 3, when, having omitted the injections for twenty-four hours, he had no attack and thereafter continued free without injections. He had also experimented with dihydroergotamine by the mouth and believed that 15 to 20 drops of D.H.E.45 taken when he felt a mild attack coming on might abort it.

The third case selected to illustrate the effects of treatment is of particular interest because the patient was a medical man, his paroxysms were especially frequent and severe, and on his own initiative he took larger doses of ergotamine tartrate than were prescribed for him without serious ill effects.

Case 7.—Male, aged 34 when first seen in August 1951, presented a written account of his illness which will be quoted *in extenso*.

"*Symptoms.*—Attacks of pain in and around left eye, radiating to left temple and occasionally to left half of palate, accompanied by lacrimation and suffusion of left conjunctiva. These attacks occur daily during the bouts and latterly they are accompanied by intense general malaise, vague abdominal discomfort, lassitude, and on three occasions by vomiting and urgent defæcation. These attacks occur in bouts, each bout lasting four to six weeks, and the bouts occur every nine to twelve months.

History of present complaint.—The onset of this pain occurred at the age of 18½ years, about fifteen years ago, and was first noticed towards the end of an Anatomy lecture, i.e. about 9.55 a.m., the pain lasting about fifteen minutes and clearing completely. It recurred the following day at precisely the same time and followed an identical course. This was repeated six days a week, omitting Sundays, and the bout lasted about a month. During the second bout, about seven months later, I was seen by a physician and an opthalmologist, and after X-rays of skull and sinuses were found to be normal, the condition was dubbed 'functional.' The bouts recurred quite regularly and during each bout the attacks followed the identical pattern, the pain being short in duration and bearable. Between the bouts, each morning on rising beads of sweat were noticed above the left eyebrow, but the general health was excellent and I took part in games, playing tennis for the University, being a member of the boxing team, and rowing, while studies were not being neglected, all exams being successfully passed with honours. As the years went on the pain in the attacks became worse and I sought the advice of a neurosurgeon, who diagnosed 'Anterior Migraine' and suggested operating on the trigeminal ganglion if the pain became disabling. I next consulted a neurologist who said he was baffled and could offer no diagnosis. (At this time X-rays of skull and cervical spine proved normal.) About two years ago I consulted another neurologist, who confidently diagnosed migraine and prescribed sedation and ergometrine (no effect). Since then I have had the attacks at their usual intervals and in the last bout, which finished three weeks ago, the constitutional upset was worse than before, but the pain was less severe."

His most recent bout had been in April and May of 1951, lasting six weeks, but had been far worse than any other for the paroxysms which had previously occurred only once in the twenty-four hours increased in frequency up to as many as six or eight. Their timing was quite haphazard. He had tried all kinds of analgesics and had sometimes given himself an injection of ergotamine tartrate when an attack started, without relief. He eventually took to using a trilene inhaler to control the pain at its worst, which was effective but made him sleepy. He was instructed when he next had a bout to use injections of ergotamine tartrate to prevent attacks. The next bout occurred in July 1952, but with an injection of 0·25 mg. at bed-time and another at midday he continued to have paroxysms at irregular intervals more than once in the twenty-four hours. He was therefore admitted to hospital, where at first he was given no ergotamine tartrate, and his attacks were observed. It was found that an injection of Pethidine 100 mg. as soon as a paroxysm began gave temporary, but incomplete, relief. He was then

given an injection of ergotamine tartrate 0·25 mg. eight-hourly and remained free from attacks on this regime for three days. Without his knowledge injections of saline were substituted, whereupon the paroxysms returned with their original frequency and severity, disappearing when the injections of ergotamine tartrate were resumed. This bout having ended, he was free until August 1953. Of this he reported as follows. "When the series began I immediately started taking 0·25 mg. Femergin intramuscularly three times a day. Within ten days I found that some attacks were breaking through the barrier, but they were not as severe as I had in the past. However, as I did not wish to be immobilized I doubled the dose, three times a day, and found that only one attack managed to get through. After about two weeks I then changed to 0·25 mg. four times a day and found that apart from some occasional discomfort in the usual situation this amount of Femergin was adequate. As the days went by I gradually reduced the frequency of the injections until I was taking only one injection each day. When I stopped altogether I found that I was getting a fairly severe generalized headache, which could be cleared by an injection of Femergin, and now I have come to the end of the series altogether. The total number of ampoules consumed was 210, but there were no toxic signs or symptoms at any time."

After complete freedom for thirteen months there was another bout, of which his account reads as follows:

"At first as usual the attacks were of moderate severity and as soon as I was certain the series had really started I began with the prophylactic Femergin injections 0·25 mg. eight-hourly. Within a week this dose was obviously insufficient as the attacks were breaking through the barrier, and I went successively on to the same dose six-hourly, and then double the dose six-hourly, i.e. 2 mg. daily by intramuscular injection. On this dose the attacks were almost controlled during the worst two weeks, but some of the side effects were rather troublesome. There was a good deal of lethargy, some anorexia and a foul taste in the mouth, with a 'thick head' most of the day. To counteract this I took 5 mg. d-amphetamine sulphate twice a day and was nearly restored to normal. All in all I had seven severe attacks break through despite this dose and then there was almost perfect control so the dose was gradually reduced and finally treatment ceased altogether. I noticed two things this time. One was that I could precipitate an attack even while on the high dose by playing my usual hard game of squash, so this activity had to be curtailed. Secondly, on ceasing treatment I noted some unpleasant release phenomena. These consisted mainly of a continual throbbing in the head, more marked on the affected side, with a generalized feeling of tremulousness. These sensations passed off after about five days, and since then I have felt perfectly normal. While I was on the high dose I did notice that my peripheral circulation was not as good as normal in that I had cold feet when the weather was not at all cold, and as this is so unusual for me it was noteworthy, but not surprising on that enormous dose of Femergin." He added that once again with the aid of the new treatment he had been able to make life bearable during the whole period.

5 patients in addition to the 3 described above were treated in similar fashion. In 2 the paroxysms were strictly nocturnal and were entirely prevented by the injection of 0·25 mg. or 0·5 mg. ergotamine tartrate at bed-time. The remaining 3 had attacks by day as well as night and were encouraged to discover for themselves the best times for the injections and the minimum dosage required. One gave himself 0·25 mg. thrice daily, another 0·5 mg. night and morning, the other 0·25 mg. at night and 0·5 mg. in the morning, and all were able to obtain

satisfactory relief with these doses. If an attack occurred the pain was of minor degree. For example, the patient already mentioned in whom an attack was witnessed (*Case* 4) reported in person twenty-four days later to state that since his first injection of 0·25 mg. ergotamine tartrate three hours after he was previously seen he had had no attack severe enough to interrupt his normal activities. He had experimented with his own dosage and found that on 0·25 mg. at bed-time and 0·5 mg. on rising he had an occasional abortive attack before his morning dose. He had been able during this period to drive his car from London to Cornwall in the day, enjoy his annual holiday and drive back to London again in one day without trouble. The bout when he was seen on the second occasion appeared to have ended.

Discussion

The particular variety of headache which is the subject of this communication was first recognized by Harris (1926), who has contributed so much to the description of neuralgic pains in the face and head. Under the heading "Periodic Migrainous Neuralgia" he refers to cases in which the attacks "may occur daily at or about the same time and last for several hours for a period of a few weeks only in the year and may recur annually at about the same time." He adds that occasionally the attacks are much shorter, lasting from 10 minutes to an hour, and may recur several times in the twenty-four hours and quotes cases to illustrate the syndrome, one of which is typical of those described in the present paper. This was the case of a man who at the age of 19 began to suffer from daily attacks, for three or four weeks every year, of severe pain in the back of the right eyeball and forehead, with lacrimation and reddening of the eye, which would last for an hour or two. Harris (1936) further described the syndrome under the title "Ciliary (Migrainous) Neuralgia." His account of the situation and character of the pain and of the associated symptoms corresponds with that described in the present paper. He does not, however, make any clear distinction between cases of this kind and others in which pain of similar distribution lasted for several hours or one or two days. The treatment he advised was alcohol injection of the Gasserian ganglion on the affected side.

Horton, McClean and Craig (1939) gave an account of 84 cases of which some probably correspond with the group now under consideration. They stress the severity of the pain, its situation mainly in and around the eye, its duration of usually less than one hour, the associated congestion and watering of the eyes and stuffiness of the nose, and the tendency for the attacks to occur at night. They state that the majority of their patients were in the fourth or fifth decades, but do not give the age of onset. Nor do they mention the duration of the bouts or describe the spontaneous remissions. They noted that in 25 cases an attack could be reproduced by an injection of histamine, and that an attack which had

begun might be controlled by the intravenous injection of epinephrine or other vasoconstricting agents and concluded that the attacks were in some way caused by vasodilatation. This led them to develop their plan of treating these patients by the method of histamine desensitization. They claimed that of their 84 patients 65 obtained permanent relief for periods of over two weeks to eighteen months.

Horton (1941) further described the syndrome. This paper was based on the observation of 72 cases. In 31 of these the pain occurred only at night " with clockwork regularity." In this paper, although the occurrence of bouts with spontaneous remissions is not included as a characteristic feature of the syndrome, the illustrative case records show that in some instances this was so. In the 5 cases quoted the onset was at the ages of 20, 30, 15, 37, and 14, which is at variance with the unsupported statement elsewhere in the paper that the malady began in the later decades of life. The value of treatment by histamine desensitization is again emphasized, but the duration of the periods for which patients were followed up is not recorded in detail.

Horton (1944) again described the syndrome, stating that the onset was often after middle age, and noted that the pain had a tendency to conform to the ramifications of the external carotid artery. Horton (1952) added little to his previous accounts, but stated that the malady chiefly affected males. He mentions that the attacks of pain tend to occur in a series and may occur repeatedly, often on a seasonal basis. He states that 95 per cent of his patients will respond to histamine desensitization, the attacks ceasing in ten to twenty days. He adds, however, that about 36 per cent of patients will have a recurrence within the first year. The average age of his patients is given as over 40.

Although many of the features of the headache described in the present communication are accurately portrayed in Horton's papers, the natural history of the untreated malady, especially the self-limited duration of the bouts, and the long intervals of freedom (often more than a year) receives little attention, and in the absence of long term follow up reports with control observations the claims made for histamine desensitization must be viewed with some doubt. In this last paper Horton (1952) observes that an attack can be promptly relieved by an intravenous injection of dihydroergotamine (D.H.E.45) and that a rectal suppository of 2 mg. ergotamine tartrate with 100 mg. of caffeine at bedtime will frequently prevent nocturnal attacks. The writer (Symonds, 1951) in describing cases 5 and 6 of the present series appears to have given the first account of the prevention of attacks by the injection of ergotamine tartrate.

Gardner, Stowell and Dutlinger (1947) described a group of cases with symptoms of the pattern under discussion. Their description of

the paroxysmal attacks corresponds with that observed by the writer, and their occurrence in bouts is noted, but there is no detailed account of the spontaneous remissions. They report briefly 13 cases, of which 10 were in males, with an average age of 34, and an average length of history of four years, the sex and age incidence of the malady thus corresponding fairly well with the present writer's observations. Impressed by the lacrimation, and congestion of the nasal mucous membrane, as objective accompaniments of the paroxysm, they advanced the hypothesis of a neuralgia of the greater superficial petrosal nerve as the cause of the attacks and proceeded to operative section of this nerve for relief. The operation abolished lacrimation on the affected side and was followed by cessation of the paroxysms for varying periods in about three-quarters of their cases. In some of these cases, however, the paroxysms did not cease until some days or weeks after the operation, and in 3 cases with relief immediately, or shortly, after the operation there was recurrence after intervals of eighteen months to three years. Gardner (1951) has recorded his later impression that even in headaches " of the typical Horton's type " about half the patients do not obtain enough relief to justify the procedure.

White and Sweet (1955) record their results from petrosal neurectomy in 6 cases described under the title of Horton's neuralgia, of which 2 appear to belong to the category under discussion. In both the bouts recurred after operation.

Kunkle, Pfeiffer, Wilhoit and Hamrick (1952) gave a clear account of the syndrome under the title "Recurrent Brief Headache of 'Cluster' Pattern" based on the observation of 30 patients, of whom 24 were males. The illness had begun between the ages of 17 and 40 in nine-tenths and between 21 and 25 in one-half. The site and character of the pain and the associated symptoms are exactly as described in the present communication. They noted in 24 cases the occurrence of the headaches in recurrent clusters of one to five in twenty-four hours for several days or weeks with symptom free intermissions lasting two months to two years or occasionally longer. In 4 of their patients an attack was rapidly terminated by the intravenous injection of ergotamine tartrate. In 2 cases a trial was made of controlled elevation of intracranial pressure by the intrathecal injection of normal saline during an attack, which failed to give relief. They concluded that dilated branches of the external carotid artery were the principal contributors to the pain. They offer critical comment on the theoretical and practical value of Horton's method of histamine desensitization in this group of cases. 11 of their patients had been treated by this method without significant benefit. They state that precipitating factors for the attacks could not be identified with certainty, though in 7 cases the headache clusters tended to follow or accompany periods of increased tension or conflict. They conclude

that the syndrome represents a migrainous variant, but make no contribution to its treatment.

In a further communication (Kunkle *et al.*, 1954) they add little of importance to the previous paper. They express the view that as the diagnostic boundaries of migraine and its variants are not clearly defined there is little justification for the segregation of "cluster" headaches as a distinct and isolated entity. With this opinion the writer's experience agrees. There are many cases of migrainous neuralgia, so called, in which the symptoms resemble those of the pattern described in this paper but are less paroxysmal, and less severe, sometimes lasting continuously for many hours, or even for days with brief intermissions. The justification for separate consideration of the attacks occurring in bouts is their susceptibility to treatment, for there is relatively little risk of toxic symptoms resulting from injections of ergotamine tartrate when given for limited periods with long intervals.

Toxic Effects of Ergotamine Tartrate

The toxic effects of ergot given as a medicine have been described ever since the drug was first used in obstetric practice for its effect upon the uterus, but it was not until ergotamine had been isolated and used extensively in the treatment of migraine that the cumulative effect of comparatively small doses of this alkaloid excited concern. Von Storch (1938) reviewed 42 cases reported up to that time in which ill-effects, including gangrene, had resulted from treatment of various conditions with ergotamine tartrate and concluded that in the presence of septic conditions or obliterative arteritis it might be a dangerous drug. His advice on dosage was that with rare exceptions no more than 0·5 mg. should be given by injection in twenty-four hours and no more than two such injections in a week. This from his data appears to have been over-cautious. Although one patient developed gangrene after taking 1 mg. orally four times in the twenty-four hours for twelve days, there had been evidence of obliterative arteritis before treatment was begun. One patient had used an average of 15 mg. per month by injection for three years without any ill-effects. Fuchs and Blumenthal (1950) recorded toxic symptoms following single large doses of ergotamine or dihydroergotamine, including in one case symptoms thought to be those of a coronary thrombosis. It is well recognized that some individuals are intolerant of the drug even in single doses. Peters and Horton (1951) state their experience of 19 patients with periodic headache who used excessive quantities of ergot preparations. 9 of these cases are recorded in detail. One patient, a woman aged 36, had taken 0·5 mg. by injection for three weeks, then three tablets daily by the mouth for six weeks, and subsequently eight tablets daily for two months. Towards the end of this time she developed

coldness, pallor and pain in the left foot with inability to move her toes, these symptoms disappearing with the cessation of treatment.

In another case the injection of 0·5 mg. daily for about three years led to threatened gangrene of a finger, and ischæmic symptoms in the toes of one foot. Against advice the patient continued with the injections, and the circulatory symptoms disappeared. Six years later though she had continued with the same daily dose examination showed no signs of peripheral circulatory disturbance.

In another patient, a man aged 56, who had taken 0·5 mg. of ergotamine daily for a year, angina of effort developed and was subsequently aggravated for half an hour after each injection. Another patient, after taking an injection of 0·25 mg. twice daily for two months, noticed pain in the forearms on using the hands, and the pulses in the radial and brachial arteries were found to be "weakly palpable." The remaining 2 patients with toxic symptoms suffered only from cramps. 3 other patients are reported as having no toxic symptoms despite large doses taken regularly for long periods, for example, 0·5 mg. twice daily for eight years (the route is not mentioned but was presumably by injection). From these observations it is evident that individual tolerance for ergotamine shows wide variations, and that provided the patient is watched for toxic symptoms and the drug is withdrawn when these appear, no irreversible damage is likely to occur.

Apart from the symptoms already recorded in *Case* 7 of this paper the writer has observed toxic effects only in one case. This was a hospital patient not included in the present series.

Case 8.—A man aged 44 had had bouts of pain beginning at the age of 32. In a bout he would have attacks of pain over the left eye occurring daily, or several times a day, for several weeks. These bouts would occur at irregular intervals of a year or more. The attacks would last from fifteen minutes to two hours, the pain being so severe that he was quite incapable of work while it lasted. He was seen as an out-patient in a particularly severe bout which had already lasted three weeks, the attacks occurring two or three times a day at irregular intervals. His doctor was advised to let him have a self-administered injection of ergotamine tartrate 0·25 mg. thrice daily, which failed to give him relief so that he remained incapable of his work as a bank clerk. He was therefore admitted to hospital, where the dose was increased to 0·5 mg. thrice daily. He was at once relieved of the attacks of severe pain, though he experienced intermittent dull headache in its previous situation. After a fortnight he was discharged home, but unfortunately the advice given to his doctor did not include two points which had been mentioned as important while he was in the ward, that in view of the large dosage of ergotamine his peripheral pulses should be watched, and that he should omit the injections for a period of twenty-four hours each week to discover when the bout had ended. Three months after his discharge he came to report that he had remained free from pain except for one mild attack lasting half an hour four days after leaving the hospital. He had, however, not omitted the injections on any day and had continued with the full dosage. For the past two months he had noticed attacks of extreme pallor in the fingers, initially only in cold weather, but latterly after

any prolonged effort with the hands as in playing golf or batting for a few minutes at the nets. Associated with this he had noticed weakness of the hands, and often pain in the forearms, and cramp in the thighs when running. On examination the radial pulses were just palpable, the brachial pulses impalpable. The pulses in the lower limbs were normal. The blood pressure was not obtainable in the arms but was 130/80 in the legs. He was instructed to discontinue the injections at once and reported a month later to state that his vascular symptoms had entirely disappeared after the injections had been stopped for two days and that he had had no recurrence of headache. His pulses were now normal. Doubtless this patient's bout had ceased long before the drug was discontinued.

Peters and Horton (1951) recommend dihydroergotamine as less toxic than ergotamine, and in their experience equally effective. The latter statement has not been borne out by the writer's experience. According to Goodman and Gilman (1955) the natural amino-acid alkaloids of ergot and specially ergotamine are highly active vasoconstrictors, the dihydrogenated alkaloids much less so. It has been shown by Wolff (1948) that the effect of ergotamine tartrate in relieving migraine headache is due to its vasoconstrictor action. Theoretically, therefore, ergotamine should be more effective than dihydroergotamine in this respect, though at the same time carrying more risk of toxic effects.

Goodman and Gilman (1955) list as contra-indications to the use of ergot preparations, sepsis, coronary disease, arterial disease and disease of the liver or kidney, and although they state that it is difficult to cause abortion with ergotamine consider that pregnancy constitutes an objection to its use.

It would appear that if these precautions are observed, together with a watch for the symptoms and signs of peripheral vasoconstriction, daily injections of ergotamine tartrate of the order described in this paper may be given over long periods without any serious toxic effects.

One further point of importance that has emerged from the present study is that ergotamine tartrate in solution is unstable, so that the preparation after a period of months may become inert. A patient who has previously obtained relief from the injections, and after an interval of freedom has another bout, may, having recourse to an unused store of ampoules, find them ineffective. This has occurred in more than one case of the present series, the subsequent use of fresh ampoules being followed by immediate relief.

Summary

(1) The analysis is presented of 17 cases in which attacks of severe pain in and around the eye occurred in bouts with long intervals of freedom. The duration of the attack or paroxysm was seldom less than half an hour or more than two hours. The frequency of the paroxysms during a bout varied from less than one to eight in the twenty-four hours. The duration of the bout was usually between two and eight weeks. The intervals of freedom lasted in most cases for more than six months and

extended up to ten years. 14 of the patients were males, and the average age at onset was 27.

(2) The successful treatment of this malady by preventive injections of ergotamine tartrate is described with illustrative cases.

(3) The relationship of the particular variety of headache described in the present paper to the descriptions given by others is discussed and the conclusion arrived at that it is a migrainous variant.

(4) The justification for regarding this variety of headache as a distinct clinical species is that since the bouts are self limited and seldom last more than eight or ten weeks they can be treated by repeated injections of ergotamine tartrate without any harmful effects of a lasting nature.

(5) The toxic symptoms that may result from the prolonged use of ergotamine tartrate are discussed with reference to the literature, and to cases observed by the writer, and the conclusion is reached that if certain precautions are observed no harm is likely to result from the administration of ergotamine tartrate in larger doses, and over longer periods, than those previously assumed to lie within the margins of safety.

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A CLINICAL SURVEY OF INTRACRANIAL ANGIOMAS WITH SPECIAL REFERENCE TO THEIR MODE OF PROGRESSION AND SURGICAL TREATMENT: A REPORT OF 110 CASES

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INTRODUCTION

IN the last quarter of a century our knowledge of the clinical and pathological features of intracranial angiomas has undergone a marked expansion. Happily similar advances in neurosurgical technique now allow the patient to profit from these gains. We now realize that far from being distinctly uncommon as was once thought, these developmental anomalies are a frequent cause of cerebral hæmorrhage and symptomatic epilepsy and are clearly of major importance. For this we are largely indebted to Egas Moniz, who in 1929 introduced cerebral angiography, and to Engerset, Lindgren and others who perfected the technique of percutaneous angiography.

Few general reviews of the condition were available in the pre-angiographic era, the classical contributions being those of Cushing and Bailey (1928) and Dandy (1928), both being based on a small series of cases. Eight years later Tönnis (1936) reported a series of 22 patients, in some of whom the pre-operative diagnosis was confirmed by angiography. However, since the Second World War, numerous papers on various aspects of the subject have been published, including general reviews by Olivecrona and Riives (1948), Mackenzie (1953) and Potter (1955).

The pathology of intracranial angiomas, recently reviewed in detail by van Bogaert (1950), has occasioned considerable dispute in the past and as a consequence their nomenclature and classification is somewhat confused and polyonymous. Synonyms in vogue include "arteriovenous aneurysm" and "angiomatous malformation" but there is little to choose

between them. Though "angioma" suggests that these lesions are tumours, it is now almost universally agreed that they are not neoplasms. Potter (1955) holds that they almost all contain abnormal arteriovenous connexions and as he points out, the way in which they become visible in angiograms supports this contention. But though this is probably true for the great majority of angiomas causing symptoms, telangiectatic malformations are perhaps an exception. These are composed of capillary and pre-capillary vessels and frequently remain symptomless, to be discovered incidentally at autopsy as Teilmann (1953) and others have shown.

This paper is but an account concerned with the clinical diagnosis and management of a series of patients with these malformations. The pathology of the lesions encountered is not discussed, and no attempt has been made to review the subject in general. It is hoped nevertheless that it will stimulate interest in the early diagnosis of these important and common intracranial lesions, for it is now evident that a substantial proportion of them can be extirpated.

Clinical Features

Clinical Material

The 110 patients under review were all seen by one of us (W. M.) in an Emergency Medical Service neurosurgical unit, in the neurosurgical department of St. George's Hospital, London, or at the National Hospital, Queen Square.

In the majority of instances the diagnosis was confirmed by angiography, though some of the earlier patients in the series were not submitted to this procedure, the diagnosis being made at operation.

In 92 patients, an angioma was found in one or other hemisphere; in one instance angiography suggested the presence of two angiomas, one in each hemisphere (*see* footnote to Table I) although some doubt was felt as to whether this was the correct interpretation of the angiogram. These angiomas were classified according to whether they were anteriorly placed (in the frontal, or fronto-parietal regions), intermediate in situation or occupied a posterior site (parieto-occipital). 17 of the 61 angiomas in the "middle" group were more or less centred on the Sylvian point. In 14 the angioma was found on the medial aspect of a hemisphere. The remainder were situated, as Table I shows, in the central regions of the brain (thalamus, internal capsules, basal ganglia and mid-brain), in the corpus callosum, posterior fossa, cavities of the lateral ventricles and orbits.

Sex and age.—63 or 57 per cent of the 110 patients in this series were males and 47 or 43 per cent were females. Olivecrona and Riives (1948) thought that angiomas were more than twice as common in males than in females, though more recently Mackenzie (1953) found an exactly equal sex distribution in his series of 50 cases. These discrepancies may

TABLE I

Site of Angioma

			Right	*Left*	*Total*	
A. Hemispheres						
1. *Anterior*	Lateral aspect	... ...	4	3*		
	Medial aspect	... ...	2	2		
			—	—	11	
2. *Middle*	Lateral aspect	... ...	18	18		
	Sylvian point	... ...	6	11		
	Medial aspect	... ...	6	2		
			—	—	61	
3. *Posterior*	Lateral aspect	... ...	7	11		
	Medial aspect	... ...	2	—		
			—	—	20	
					—	92
B. Central site (Thalamus, basal ganglia and mid-brain)						
	Lateralized	... ...	3	5		
	Mid-line ...	... ...		1		
			—	—	—	9
C. Corpus callosum	... ...					†3
D. Posterior fossa	... ...					3
E. Intraventricular	... ...					2
F. Orbital	... ...					1
						—
					Total	110

*Included 1 patient who possibly had a second angioma in the other hemisphere.
†Includes 1 patient who also had an orbital angioma.

be attributable to the age of distribution of their patients, for Table III shows that in the present series there was a much greater preponderance of males among the younger patients at the time of diagnosis. Of 51 patients who were under thirty at this time 33 were males and only 18 were females. The sex distribution was exactly equal in the remainder.

TABLE II

Age at onset of first symptom (109 *patients**)

	Males	*Females*	*Total No.*	*Per cent*
0–9 yrs.	7	4	11	10
10–19 yrs.	18	20	38	35
20–29 yrs.	20	6	26	24
30–39 yrs.	13	10	23	22
40–49 yrs.	1	6	7	6
50–59 yrs.	3	1	4	3
	—	—	—	
	62	47	109	

*The age at onset was not known in one patient.

Age at onset of symptoms.—The average age at the onset of symptoms was 24 years and nearly 70 per cent of patients had their first symptoms before they were 30 the majority in their second or third decades. The

youngest patient at this time was an infant of one who commenced having seizures which were later found to have focal features; the oldest a man of 57 noticed as his first symptom the onset of numbness of the left fingers at this age.

TABLE III

Age at diagnosis (109 *patients**)

	Males	*Females*	*Total No.*	*Total Per cent*
0–9 yrs.	1	1	2	2
10–19 yrs.	12	8	20	18
20–29 yrs.	20	9	29	27
30–39 yrs.	15	10	25	23
40–49 yrs.	8	15	23	22
50–59 yrs.	5	4	9	8
60 and over	1	—	1	—
	62	47	109	

*The age at diagnosis is not known in one patient.

Age at diagnosis.—The average age at the time the diagnosis was established was some thirty two years though, as Table III indicates, nearly a third of the patients were 40 or over. The two 9-year-old children were the youngest patients to be diagnosed in this series whilst the eldest was a man of 64.

It will be seen that the average duration of symptoms before diagnosis was about eight years for the whole group.

The Principal Symptoms

A detailed discussion of the general symptomatology of intracranial angiomas is unnecessary for the subject has recently been fully dealt with by Mackenzie (1953) and other writers. The cardinal symptoms in the majority are those due to a subarachnoid or intracerebral hæmorrhage, with or without epilepsy and periodic headaches with a migrainous character. Nevertheless some angiomas, particularly those in uncommon situations, cause what might be called atypical symptoms which may give rise to diagnostic errors. These will be considered in more detail later.

The Initial Symptom

Table IV indicates the nature and relative frequency of the initial symptoms of the patients in our series and in those reported previously by Mackenzie (1953) and Olivecrona and Riives (1948). It will be apparent that symptoms of hæmorrhage were more frequently encountered in our series than in the others, while epilepsy and periodic headaches were less common initial complaints.

TABLE IV
The initial symptom

	Present series (110 *patients*)		*Mackenzie* (1953) (50 *patients*)		*Olivecrona and Riives* (1948) (43 *patients*)	
	No.	*Per cent*	*No.*	*Per cent*	*No.*	*Per cent*
Hæmorrhage—						
Subarachnoid 42 Intracerebral alone 4	46	42	15	30	17	40
Epilepsy	29	26	16	32	17	40
Periodic migrainous headaches	16	15	12	24	—	
Progressive hemiparesis	8	7	6	12	—	
Headaches	7	6	—		—	
Ocular symptoms	2		1		—	
Sensory limb complaints	1		—		—	
Deafness	1		—		—	
	110		50			

CARDINAL SYMPTOMS

(*a*) *Symptoms of hæmorrhage.*—As Table IV shows these were the commonest initial symptoms in this series and were encountered in 46 patients or 42 per cent of the total. In 42 instances a subarachnoid hæmorrhage, which was often confirmed by lumbar puncture, occurred with or without signs indicative of an associated intracerebral hæmorrhage, but in an additional 4 patients the evidence favoured the latter happening alone.

The youngest patient to develop a hæmorrhage was eight years old at the time, the oldest being 55. On an average these 46 patients were about 25 years old at the time of their first hæmorrhage (19 being under 20) and came to be diagnosed some two years later. In this interval 9 patients developed epilepsy and 1 periodic headaches.

Not infrequently multiple small hæmorrhages occurred without grave sequelæ. In all, 17 patients had more than one subarachnoid hæmorrhage before diagnosis, 3 having three hæmorrhages, 2 having four hæmorrhages and 1 no less than six separate "leaks" from the malformation: yet the latter patient was well and free from abnormal neurological signs at this time. These numbers strengthen the impression that a subarachnoid hæmorrhage from an angioma is much less likely to be fatal than one due to a ruptured intracranial aneurysm.

Altogether 60 patients (36 males and 24 females) or over half the total had a hæmorrhage before diagnosis, 16 having in addition seizures (which preceded the first hæmorrhages in 8 instances) and 8 periodic migrainous headaches, preceding the first hæmorrhage in 7. Symptoms pointing to an intracerebral bleed without associated subarachnoid hæmorrhage arose in 7 instances in all and, as has already been mentioned, in 4 they constituted the first manifestation of the disorder.

(*b*) *Epilepsy*.—In this series epilepsy was the second commonest initial symptom, 17 males and 12 females or 26 per cent of the total presenting in this manner. The youngest patient to develop epilepsy was a one-year-old child, the oldest a man of 45 who had five major seizures in the ensuing two years and was investigated for epilepsy of late onset at the age of 50. The average age at which the first seizure occurred was 22 but a period of twelve years elapsed on an average before the diagnosis was established. Meanwhile 6 had a hæmorrhage and 1 developed periodic migrainous headaches. This average interval, it will be seen, is appreciably longer than that obtaining for patients whose first symptoms were due to a hæmorrhage.

51 patients in all had seizures at one time or another before diagnosis, 16 having one or more hæmorrhages in addition and 11 periodic migrainous headaches. 15 of the total with epilepsy had generalized convulsions alone, 10 had both focal and generalized attacks and 26 focal seizures only. Unfortunately the information available concerning the nature of the seizures is rather scanty in some instances. It will be recalled, however, that Mackenzie (1953) found that with one exception all the patients in his series who initially developed epilepsy had at some time or another attacks displaying focal features.

(*c*) *Periodic migrainous headaches*.—This term is used to describe the type of headache experienced by a substantial proportion of patients with intracranial angiomas as it indicates that the symptoms more or less resemble true migraine without implying that the two are identical. Mackenzie (1953) notes that this symptom-complex is usually distinguished from "idiopathic" migraine by the character of the pre-headache sensory or motor phenomena and the temporal relationship of the latter to the subsequent head pains which are either bilateral or strictly limited to the site of the angioma. Nevertheless it is our experience that, initially at any rate, this symptom is often indistinguishable from true migraine and that it usually commences at about the same age as the latter. In a few instances moreover it has persisted after the angioma has been completely extirpated, a phenomenon which Olivecrona and Riives (1948) observed in one of their patients.

As Table IV shows this symptom was the third commonest initial manifestation in the series, being present in 16 or 15 per cent of patients, 7 of whom were males and 9 females. The age at onset ranged from between 4 and 34 years, being 13 on an average. A mean period of twenty years elapsed before these patients came to be diagnosed during which time 6 had a subarachnoid hæmorrhage and 9 commenced to have fits. Although 4 had migrainous headaches only prior to admission to hospital there were atypical features in each case, 2 patients for example having had permanent hemianopic defects for years. Two further patients also had periodic migrainous headaches, but in their case they were preceded

by seizures in one and by a hæmorrhage in the other. This symptom then, when present, usually preceded all others and often by many years.

It is of some interest to note that in one-third of the patients who had periodic migrainous headaches a family history of migraine was obtained, as compared with approximately 9 per cent for the whole series. While the familial incidence of true migraine in those who have the condition is considered to be about 60 per cent these figures suggest that in patients with intracranial angiomas periodic migrainous headaches are not always directly due to the effects of the angioma alone, but may at times be attributable to coexistent structural and functional liabilities which are in some degree interdependent.

Less Common Symptoms

Among these only two need be discussed, that of a progressive hemiparesis and headaches which do not resemble migraine.

Progressive hemiparesis was the presenting complaint of 8 patients only. The symptom was gradual in onset and was unaccompanied by features suggestive of an intracerebral hæmorrhage. 4 of these patients had parietal or fronto-parietal angiomas with an average age at onset of 26 years and at diagnosis of 37 years, while the remaining 4 patients who had central angiomas were 20 years old on an average at the onset of their complaint and 30 when the diagnosis was established. In all but one of the 9 patients other symptoms, notably fits and hæmorrhages, appeared though it is of note that many years often elapsed (twenty years in one instance) before this happened. Furthermore as the disability was often confined to one limb (usually an arm) for a long time it is not surprising that these patients were frequently misdiagnosed. For example one was thought to exhibit the scalenus anticus syndrome, another to have syringomyelia and a third disseminated sclerosis.

Headaches.—7 patients in the series initially complained of headaches of a nature different from the periodic migrainous variety already mentioned. The nature of this complaint varied from patient to patient so that from this point of view they do not form an homogeneous group. In every instance, however, the symptom ensued at a much later age than did periodic migrainous headaches, the average age at onset being 33 years. In one patient with a posterior fossa angioma the headaches were probably due to internal hydrocephalus; in another to distortion and displacement of pain-sensitive intracranial structures by a large intracerebral hæmatoma. A third patient whose principal complaint was that of a persistent pain localized to the region of the right orbit was found to have an angioma at the Sylvian point on the same side.

The Principal Signs

This section is concerned with the principal physical signs present at the time the diagnosis was confirmed by angiography or at operative

exposure of the malformation. Naturally these signs were often transient in appearance and occasionally there was a history of abnormal signs being elicited at one time although these subsequently disappeared before the diagnosis was made.

Intracranial bruit.—This important sign was definitely elicited in 39 or 38 per cent of the 103 patients in whom its presence or absence was noted in the case records. A bruit was heard in 67 per cent of those whose initial symptom was that of periodic migrainous headaches, 50 per cent of those with epilepsy and in only 12 per cent of patients who had a hæmorrhage as the initial manifestation. All patients with bruits had large angiomas with the sole exception of one patient who had a small orbital angioma. By comparison, of those in whom no bruit was heard 46 had large and 54 small angiomas. When the presence or absence of this sign was correlated with the situation of the angioma in relation to the surface of the brain it was found that in 52 instances in which the angioma was largely situated on the surface, a bruit was heard in 14 and not heard in 38. Conversely when the angioma was largely buried in the depths of the brain, as was found to be the case in 47 patients, a bruit was heard in 22 and not heard in 25. In the remaining 11 patients in the series the evidence as to the relationship of the angioma to the brain surface was inconclusive.

It is concluded then that the size of the angioma rather than its situation in relation to the brain surface is of significance in determining the presence or absence of this sign. Mackenzie (1953) noted that a bruit was elicited in a half of the patients in his series but was rare where hæmorrhage had been the presenting symptom. Our findings are in accord with this observation for, as will be seen, the latter group of patients had smaller angiomas on an average than those presenting in other ways.

Focal neurological signs.—The extent and nature of the focal neurological signs noted at the time of diagnosis will not be discussed in detail. When present, as they were in 69 per cent of patients they were readily explicable when related to the site of the angioma. In 6 patients one or both limbs contralateral to the angioma were observed to be smaller than the corresponding limbs on the other side. In 3 the contralateral arm and hand were affected together with a reduction in size of the face and head on that side in one patient, while in the others the contralateral arm, hand, leg and foot were all involved. In 5 of the 6 patients the angioma, in all cases a large one, was parietal or fronto-parietal in site, the remaining individual having a thalamic angioma which had extended outwards to some extent into the neighbouring hemisphere.

In all 6 there were other lateralizing neurological signs although they were minimal in 3 patients. The average age at onset of symptoms in these patients was thirteen years and the average duration eleven before diagnosis.

Some 34 patients or 31 per cent of the total had no focal neurological signs at the time of diagnosis although 10 had audible intracranial

bruits. As the initial symptoms in this group were those of a hæmorrhage in 15, epilepsy in 8 and periodic migrainous headaches in a further 8 patients, it is evident that a third of all patients whose initial symptoms were due to hæmorrhage, a quarter of those who had seizures initially and half of those whose disorder commenced with periodic migrainous headaches, had no focal neurological signs when the diagnosis was established.

Papillœdema.—17 of the patients in this series were found to have papillœdema on admission to hospital although in 14 this sign was clearly related to a recent intracerebral or subarachnoid hæmorrhage. One patient with papillœdema had a large occipital angioma which was presumably acting as a space occupying lesion of some considerable size as there were radiological signs of raised intracranial pressure, while another had well marked internal hydrocephalus due to obstruction of the cerebrospinal fluid pathways by a cerebellar angioma. It is evident that papillœdema is neither a common nor a conspicuous sign though it may develop after a cerebral hæmorrhage.

Dementia.—On admission to hospital 16 patients showed definite organic intellectual changes which were probably hydrocephalic in origin in 2 patients with posterior fossa angiomas. 11 of the remaining 14 had focal neurological signs and 6 had intracranial bruits in addition but 3 demented patients had neither and they presented as long standing epileptics with dementia but without any physical signs. 12 of these 14 patients with dementia had large angiomas which had caused symptoms for eighteen years on an average, but in only one instance were there any secondary cardiovascular changes suggestive of a large arteriovenous shunt. Olivecrona and Riives (1948) stated that 50 per cent of their patients had mental changes although they were but slight in half of this number. They suggested that the most important cause of this complication was progressive cerebral atrophy associated with short circuiting of the cerebral circulation through the angioma and they found pneumoencephalographic evidence of general or local cerebral atrophy in 17 of their patients. Unfortunately none of the patients with dementia in this series were subjected to air studies.

Associated cardiovascular abnormalities.—It has been known for a long time that intracranial angiomatous malformations may eventually lead to secondary cardiovascular effects, the angioma acting as a large arteriovenous shunt. These include a rising pulse pressure, left sided cardiac hypertrophy and, in severe examples, cardiac failure. These important complications were rarely encountered in the present series presumably because many of the angiomas were relatively small. There were, however, 9 patients who showed evidence of such changes; that is to say they had raised pulse pressures and clinical or radiological evidence of enlargement

of the heart to the left. In one instance cardiac catheterization revealed an abnormally high oxygen content in the venous blood entering the heart. This patient, a woman aged 43, complained of epilepsy with left sided focal features of thirteen years duration. On examination she was found to have a severe left hemiparesis with sensory changes and slight wasting of the left hand but she showed no evidence of intellectual impoverishment. There was an audible bruit over both sides of the skull, though it was most marked in the right fronto-parietal region. Her skull X-rays were normal, but chest X-rays showed evidence of left sided cardiac enlargement. Her blood pressure was 120/65. A right carotid angiogram revealed an enormous angioma in the right Rolandic region.

All 9 patients had large angiomas and 8 had audible intracranial bruits. Only one patient, however, showed organic intellectual changes. In 6 instances the angioma was found to occupy a "middle" hemisphere site; in one it was situated in the corpus callosum and in two it was located in the parieto-occipital region.

Radiological Features

(1) *Plain radiography*.—The results of this procedure were noted in the case records of 101 patients in this series. In 62 they were considered to be normal and in 39 abnormal in some way. In 24 of the latter abnormal intracranial calcification was demonstrated. On the basis of these findings it is evident that the majority of patients with intracranial angiomas have normal skull radiograms, only a quarter of patients in this series showing radiological evidence of calcification in the malformation.

(2) *Angiography*.—The diagnostic value of this procedure in relation to intracranial angiomas is now well known and needs no further emphasis. There were only 7 patients in this series who were not submitted to angiography, and in the remaining 103 patients the diagnosis was confirmed by this procedure.

(3) *Encephalography and ventriculography*.—One or other of these investigations was performed successfully in 21 patients, abnormal findings being obtained in 18 or 86 per cent. One of these latter patients had a posterior fossa angioma and the ventriculogram showed all three supratentorial ventricles to be markedly dilated. In the remainder a definite filling defect or other evidence of a space occupying lesion was demonstrated at the site of the angioma. Only 8 of these 17 patients had a definite subarachnoid or intracerebral hæmorrhage previously and 7 showed no focal neurological signs when the investigation was made. 13 of the 17 angiomas in question were considered to be large ones. It is reasonable to conclude that even apparently unruptured angiomas occupy an appreciable amount of intracranial space much as tumours do; that they have other features in common will be demonstrated later in this paper.

Associated Vascular Anomalies and Complications

(1) *Circoid aneurysms of the scalp.*—These anomalies are found in the distribution of the external carotid artery but Olivecrona and Riives (1948) noted that the branches of the corresponding internal carotid artery were equally involved. 5 patients in their series showed marked dilatation of the external carotid vessels on one side; 2 had no cerebral symptoms but both proved to have intracranial angiomas as did the others. In the present series there was only one patient who demonstrated this feature:

A man of forty-nine had had a pulsating swelling over the vertex which had throbbed when he was worried for as long as he could recall. After a subarachnoid hæmorrhage when he was twenty-one he developed epilepsy. The circoid aneurysm of the scalp was observed when he was admitted to hospital on that occasion. When readmitted recently the vascular malformation of the scalp was found to be supplied by grossly enlarged occipital arteries and a loud bruit was heard over both occipital and carotid vessels as well as over the circoid aneurysm. He was mildly dysphasic and demented and had a minimal right sided hemiparesis with a lower right quadrantic homonymous field defect. Carotid angiography demonstrated a large intracranial angioma in the region of the left Sylvian fissure.

As Potter (1955) has remarked, increased extracranial vascularity is an uncommon feature and is quite unreliable as a diagnostic sign in view of its rarity.

(2) *Intracranial aneurysms.*—4 patients in this series were thought to have true intracranial arterial aneurysms in addition to their angiomas. The adjective "true" is used to distinguish them from the pseudo-aneurysmal formations which may develop from an angioma.

The first patient had a right parieto-occipital angioma and a right carotico-cavernous fistula. For many years she had experienced periodic migrainous headaches with lancinating pains in the right cheek. Latterly her facial pain, which was associated with a unilateral watery nasal discharge on the same side, had become the most prominent symptom. Although she had no physical signs other than a right orbital bruit it was thought that the carotico-cavernous fistula might have accounted for the pain in her cheek which had troubled her so much.

The second patient who gave a history of fits over the previous year also had no abnormal neurological signs. Angiograms demonstrated an angioma at the left Sylvian point with multiple small aneurysms on both the anterior and middle cerebral arteries on that side. He subsequently died elsewhere and it is not known whether the aneurysms contributed to the fatal issue as no autopsy was performed.

The third patient had a large right parietal angioma and two aneurysms on the dilated right internal carotid artery. She had previously had three subarachnoid hæmorrhages but it could not be ascertained whether the aneurysms had been responsible for any of these episodes.

The remaining patient, however, died from a ruptured aneurysm which was found at autopsy to be situated on the right posterior inferior cerebellar artery. The angioma in this case lay in the left cerebellar hemisphere and may have been responsible for the hæmorrhage he had suffered a year previously.

The association of cerebral aneurysms with angiomas demonstrated by these 4 patients does not of course contribute to the current controversy as to whether intracranial aneurysms are congenital in origin or develop

as a result of local pathological changes secondary to hypertension, atherosclerosis, etc. All 4 patients were adults of from 36 to 54 years of age at the time of diagnosis and although none of them had a high blood pressure, it is reasonable to suppose that the increased intracranial blood flow consequent upon the presence of an angiomatous malformation had thrown abnormal stresses on the cerebral vessels in question.

(3) *Subdural hæmatomas.*—3 patients, all operated upon, were found to have chronic subdural hæmatomas in association with an angioma. In 2 instances the subdural clot was overlying an intracerebral hæmatoma but in the third patient a subdural hæmatoma was found over Broca's area in the left frontal lobe while the angioma, which lay in the wall of a large intracerebral hæmatoma, was situated on the medial aspect of the frontal pole of the same hemisphere. The patient had had a subarachnoid hæmorrhage three weeks previously and his subsequent head pain was principally located in the left temple.

All 3 patients had suffered recent subarachnoid hæmorrhages but 2 of them had no localizing signs. It is reasonable to suppose that if they had been treated conservatively and not submitted to angiography their subdural hæmatomas would ultimately have given rise to further symptoms.

The Size of the Angioma

Although invaluable in the diagnosis and location of angiomas, angiography does not always provide an indication of their size. No attempt has been made to classify by size those in this series other than by grouping them into "large" and "small" lesions. This was found possible in 109 patients with the result that 70 or 64 per cent were considered to have large and 39 or 36 per cent small malformations.

In the light of this information the question was posed as to whether the mode of presentation as indicated by the initial symptomatology had any bearing on these findings. Accordingly cases presenting with one of the cardinal symptoms were analysed from this point of view (Table V) and it will be seen that those patients who initially had epilepsy or periodic migrainous headaches were much more likely to have large angiomas than those whose first symptoms were due to hæmorrhage.

Table V

Size of angioma in relation to initial symptoms

Initial symptoms	*No. of patients*	*Size of angioma*	
		Large	*Small*
		Per cent	
Hæmorrhage	46	46	54
Epilepsy	29	76	24
Periodic migrainous headaches	16	88	12

It will be recalled that patients presenting initially with a hæmorrhage were diagnosed at an earlier age than the others, averaging 27 as compared

with 34 for those with epilepsy and 33 years of age for those with periodic migrainous headaches. Furthermore their duration of symptoms (as indicated by the time which elapsed between their first symptom and the time of diagnosis) was much shorter being on average two years as compared with twelve years for those presenting with epilepsy and twenty for those with periodic migrainous headaches. It might be thought then that the age of diagnosis and the duration of symptoms would account for differences in size of the angioma in relation to the initial symptoms. Tables VI and VII indicate the findings when these patients were re-grouped in relation to these two factors.

TABLE VI

Size of angioma in relation to age at diagnosis and initial symptoms

Initial symptoms	*No. of patients*	*Size of angioma*			
		Large		*Small*	
		No.	*Per cent*	*No.*	*Per cent*
Hæmorrhage					
under 30 at diagnosis	28	12	43	16	57
30 and over	17	9	53	8	47
Epilepsy					
under 30 at diagnosis	9	7	78	2	22
30 and over	20	16	80	4	20
Periodic migrainous headaches					
under 30 at diagnosis	7	6		1	
30 and over	8	7		1	
All patients					
under 30 at diagnosis	51	30	59	21	41
30 and over	57	40	70	17	30

TABLE VII

Size of angioma in relation to duration of symptoms and initial symptoms

Initial symptoms	*No. of patients*	*Size of angioma*			
		Large		*Small*	
		No.	*Per cent*	*No.*	*Per cent*
Hæmorrhage					
5 years or under before diagnosis	36	14	39	22	61
Over 5 years ,, ,,	10	7	70	3	30
Epilepsy					
5 years or under before diagnosis	8	5	63	3	37
Over 5 years ,, ,,	21	18	86	3	14
Periodic migrainous headaches					
5 years or under before diagnosis	2	2		0	
Over 5 years ,, ,,	13	11		2	
All patients					
5 years or under before diagnosis	55	26	47	29	53
Over 5 years ,, ,,	53	45	85	8	15

From Table VI it will be seen that for all patients presenting with cardinal symptoms there is a proportionately slight increase in the size of the angioma in relation to the age of diagnosis, 59 per cent of patients

having large angiomas when under 30 years of age at diagnosis as compared with 70 per cent for those who were over 30 at this time. A similar slight increase is also seen among those who initially had a hæmorrhage but not apparently among those with epilepsy or periodic migrainous headaches. When only the younger patients (under 30 years of age) are considered those presenting with hæmorrhage are still more liable to have small angiomas when they come to diagnosis than those presenting with epilepsy or periodic migrainous headaches. Considering the second factor, the duration of symptoms, Table VII shows that a substantial proportionate increase in size of the malformation occurs in those whose symptoms commenced more than five years before diagnosis as contrasted with those who had symptoms for a shorter period. Thus 85 per cent of the former and 47 per cent of the latter had large angiomas. This tendency is also seen in those who initially had a hæmorrhage or developed epilepsy though the number of those presenting with periodic migrainous headaches was too small to be of comparative value for there were only two patients who had such symptoms for five years or less. These figures nevertheless suggest that in patients who present initially with a hæmorrhage or with epilepsy the angioma tends to grow in size subsequently. This aspect will be considered in greater detail later.

It is generally agreed that intracranial angiomas are congenital malformations but understandably there is no information available as to their size when they start to cause symptoms. The evidence summarized above suggests that whereas the majority of angiomas which first betray their presence by hæmorrhage are small in size at the onset of symptoms, those initially causing fits or periodic headaches tend to be much larger malformations.

The situation of the angioma in relation to the cortex.—It is well known that while some angiomatous malformations are largely situated on the brain surface others lie buried deep within the brain and may be quite invisible when the cortex is inspected at operation. There was an approximately equal distribution of the angiomas in this series into the two groups, for of 105 patients, 55 had predominantly surface angiomas and 50 more deeply lying ones.

It might be thought that the situation of the angioma as defined above would have a bearing on the clinical presentation; in fact MacKenzie (1953) found that the 12 patients in his series who initially had a subarachnoid hæmorrhage tended to have more deeply placed angiomas in contrast with those who presented with epileptic fits. Our figures do not bear out this contention for, as Table VIII shows, the angiomas were about equally distributed between the two groups in patients presenting with hæmorrhage, epilepsy and periodic migrainous headaches.

It should be noted, however, that the majority of patients whose initial symptom took the form of a progressive hemiparesis had deeply placed

TABLE VIII

Situation of the angioma in relation to the cortex and the presenting symptoms

Presenting symptoms	*No. of patients*	*Superficial angiomas Per cent*	*Deep angiomas Per cent*
Hæmorrhage	46	57	43
Epilepsy	29	56	44
Periodic migrainous headaches	16	56	44
Progressive limb weakness	8	25	75

malformations; in fact in 4 of these 8 patients they were situated in the thalamus, basal ganglia or mid-brain.

The Symptomatology of Intracranial Angiomas in Relation to their Site

(1) *Hemisphere angiomas.*—It will be recalled that 92 patients in this series had hemisphere angiomas; their principal symptoms and signs are summarized in Table IX.

TABLE IX

The symptomatology of hemisphere angiomas

Site	*Anterior*	*Middle*	*Posterior*	*Medial aspect*
Number of cases	11	61	20	14
Sex	5 males 6 females	35 males 26 females	11 males 9 females	8 males 6 females
Mean age at onset of symptoms	28 years	23 years	21 years	21 years
Mean age at diagnosis	32 years	31 years	34 years	27 years
Average duration of symptoms before diagnosis	4 years	8 years	13 years	6 years
Initial symptoms		*Percentage of cases*		
(*a*) Hæmorrhage	73	34	50	79
(*b*) Epilepsy	9	39	15	7
(*c*) Migrainous headaches	9	13	30	7
Initial and subsequent symptoms together				
(*a*) Hæmorrhage	73	52	65	86
(*b*) Epilepsy	45	61	40	50
(*c*) Migrainous headaches	9	13	45	14
Focal signs present at diagnosis	56	69	70	64
Dementia	9	15	12	29
Audible intracranial bruit	9	44	35	21
Size of angioma				
(*a*) Large	36	67	70	50
(*b*) Small	64	33	30	50
Situation of angioma				
(*a*) Largely superficial	73	59	63	64
(*b*) Mainly deep	27	41	37	36

Symptoms of hæmorrhage, it will be seen, were most commonly due to anteriorly or medially placed angiomas, approximately three-quarters of them presenting in this way. By contrast posterior angiomas were less likely to bleed, though over a half did so before the diagnosis was established.

Epilepsy was most frequently encountered in the middle group as Mackenzie (1953) has already noted and was a comparatively uncommon initial symptom of angiomas elsewhere in the hemispheres.

Periodic migrainous headaches on the other hand were usually associated with posteriorly situated angiomas, being an uncommon feature of anterior ones.

The average duration of symptoms before diagnosis varied considerably in the different situations and ranged from four years with anteriorly placed hemisphere angiomas to thirteen years with posterior lesions. Probably these differences are related to the frequency with which the cardinal symptoms were encountered, for patients presenting with periodic migrainous headaches do not as a rule come to diagnosis before many years have elapsed in marked contrast with those who initially have a subarachnoid hæmorrhage.

The physical signs elicited when these patients came to be diagnosed need little comment. *Focal signs* were encountered with approximately the same frequency in all four groups of hemisphere angiomas but for some reason those situated on the medial aspects of the hemispheres are more likely to be associated with *dementia* than those elsewhere. *Intracranial bruits* were heard more frequently in patients with posteriorly situated angiomas than with the others, but the former tended to be larger in size than elsewhere. There appeared to be little correlation between the hemisphere site of an angioma and the frequency with which it lay on or near the surface or was to a greater extent found in the depth of the brain.

(2) *Central angiomas*.—The symptomatology of central angiomas or those involving the thalamus, basal ganglia, internal capsules and mid-brain have already been discussed by one of us (Paterson, 1955) previously. In brief there were 9 patients in this series 7 males and 2 females, who had central angiomas. The average age at onset was 22 and, at diagnosis, 27 years. The commonest initial symptom was that of a progressive hemiparesis and 5 patients presented in this way; 3 others had a subarachnoid hæmorrhage initially and one developed fits. However, when all symptoms experienced up to the time of diagnosis are considered 7 of the 9 patients had one or more hæmorrhages (with a total of 12 separate incidents), 5 developed a progressive hemiparesis and only the one patient mentioned above had fits. None of the patients in this group had periodic migrainous headaches. In short, whereas central angiomas tend to bleed just as frequently, if not more so, than those elsewhere, progressive

hemiparesis is a much commoner presenting symptom in this group. Conversely epilepsy and periodic migrainous headaches are much rarer.

By the time the diagnosis came to be established all 9 patients exhibited focal signs. 8 had a hemiparesis of greater or lesser degree with associated hemisensory defects in 4 and hemianopic visual field defects in 3. One of these 8 patients was observed to have involuntary movements of an athetoid type affecting the hemiparetic limbs. 5 patients had focal signs which by their nature suggested the location of their lesions. These included vertical gaze palsies in 3, pupillary abnormalities in 3, ptosis and external ocular palsies in 4 and nystagmus in one instance. One patient was regarded as showing evidence of organic intellectual deterioration. An intracranial bruit was heard in only 2 patients though in 5 the malformation was considered to be of large size.

(3) *Posterior fossa angiomas.*—The symptomatology of anterio-venous malformations at this site has recently been described in detail by Logue and Monckton (1954). Of their 9 personal cases 2 had cerebellar angiomas which bled and 7 had brain-stem lesions which gave rise to a subarachnoid hæmorrhage, slowly progressive neurological disablement, or to acute hydrocephalus by obstruction of the cerebrospinal fluid pathways. 2 of the 3 patients in the present series who had posterior fossa angiomas were very similar to Logue and Monckton's 2 patients with cerebellar angiomas but both were gravely ill on admission and died shortly afterwards from hæmorrhage. The third patient, however, showed some features which were not apparently seen in their series.

She was a woman of 46 who gave a seven-year history of left sided deafness, intermittent diplopia, headaches, deteriorating memory and, latterly, an ataxic gait. On admission she was found to have a cerebellar dysarthia, nystagmus, marked ataxia of the left limbs and evidence of involvement of the left fifth and seventh nerves together with a severe left-sided nerve deafness and loss of the left caloric responses. Her cerebrospinal fluid at lumbar puncture contained 800 mg. of protein per 100 ml. and a ventriculogram showed gross internal hydrocephalus of the lateral and third ventricles as well as dilatation of the aqueduct. Stereo-radiograms of the petrous bones revealed a large cavity below the fundus of the left internal auditory meatus. These finding were considered to be very suggestive of a large cerebellopontine angle tumour but at operation a typical angiomatous malformation was found in the left cerebellar lobe which was amputated. No angiograms were performed so the true extent of the angioma is not known. Subsequently her physical signs were unchanged, though her general condition improved and six years later she was still able to walk with the aid of a stick.

(4) *Angiomas of the corpus callosum.*—There were 3 patients in this series, one male and two female with angiomas at this site but one patient had a co-existing orbital angioma which accounted for the symptomatology in his case. The only important symptoms in the other 2 patients were those of hæmorrhage and one had had four separate incidents of this order and the other two before diagnosis. One patient showed a mild inco-

ordination of an arm but the other was free from neurological signs, though both had an audible intracranial bruit. In both instances the malformations were deemed to be large in size as judged by the angiographic appearances.

(5) *Intraventricular angiomas.*—Two patients had angiomas which were located in one lateral ventricle. Both presented with "subarachnoid" hæmorrhage and in neither instance were any abnormal physical signs found on examination other than those associated with such a hæmorrhage. One patient had suffered infrequent attacks of migraine which in retrospect could not be distinguished from "idiopathic" hemicrania but the other had been well before the ictus. A lumbar air encephalogram was performed on one of these patients and showed a ventricular filling defect in the situation of the angioma. It is interesting to note that in these 2 instances as with other patients in this series (notably those with central angiomas) intraventricular bleeding did not give rise to any more grave effects than those usually encountered with true subarachnoid hæmorrhages.

(6) *Orbital angiomas.*—Two patients had arteriovenous malformations involving the orbit although one of them had a second angioma which lay in the corpus callosum but which had been symptomless up to the time of diagnosis. The symptomatology of both these patients was very similar and commenced in the third decade. Both men complained of increasing proptosis of the affected eye associated with reddening of the globe and were troubled by a pulsating bruit referred to the ear on the same side. When they came to diagnosis three and seven years respectively after the onset of symptoms, the abnormal findings were largely confined to the orbits involved. In each case there was well marked proptosis with downward displacement of the globe, a proptosis which was definitely pulsatile in one instance. A bruit was heard over the affected eye in both patients and in one, the right temporal scalp vessels were dilated and tortuous. In both the retinal veins were engorged and in one the retinal arteries were tortuous. There was doubtful papillœdema in the affected eye in one patient.

The Outcome

In assessing the relative value of different forms of treatment for any condition one should have adequate numbers of patients in each treatment group who are more or less equally distributed in regard to age, sex and any other factors which might be expected to influence the outcome. It will also be necessary to include in the series an appropriate number of untreated patients as controls if the natural outcome of the condition is not known with a fair degree of certainty. For obvious reasons, however, a planned trial of this nature cannot be undertaken with patients who have intracranial angiomas, many of whom present in a state which demands urgent surgical intervention.

73 patients received some form of surgical treatment, radiotherapy or a combination of the two. The remaining 37 were for various reasons given no treatment other than that undertaken to provide symptomatic relief, such as the control of epilepsy. The different forms of treatment used are summarized in Table X each patient receiving that which was

TABLE X

Treatment

Total excision	36
Ligation of cortical vessels	
alone—15	
followed by radiotherapy—1	16
Ligation of common carotid artery	
alone—4	
followed by radiotherapy— 2	6
Exploratory craniotomy	
alone—7	
followed by radiotherapy—2	9
Radiotherapy	
alone—6	
after surgery—5	11
No surgical treatment or radiotherapy	37

considered most suitable at the time though understandably opinion on this matter has altered radically over the decade covered by this series. In short the patients in each treatment group were highly selected; any comparative assessment of the outcome therefore can only be made with considerable reservations.

Lack of accurate information concerning the natural outcome of the condition constitutes another aspect of the problem, for many of the prognostic opinions in the literature are largely based on experience acquired in what might be termed the pre-angiographic era. It is now evident that many patients with cerebral angiomas escaped diagnosis in those days while on the whole too little time has since elapsed to allow any firm conclusions to be established. It might not be unprofitable nevertheless to consider firstly what happened to the untreated patients in this series before noting the results of the surgical and radiotherapeutic measures adopted in others.

UNTREATED PATIENTS

We have thought fit to consider along with the 37 untreated patients a further 5 who had an exploratory operation which was not followed by any specific procedure such as arterial ligation or by radiotherapy. In all, then, there were 42 patients in this group. 3 died in hospital before or shortly after diagnosis and 8 were not subsequently followed up, though it is of some interest to note that while they had had symptoms for an average of fifteen years, only half of them were in any way incapacitated when diagnosed. 3 of the remaining 31 patients died later and the rest,

who experienced symptoms for an average of seven years, were followed up for a corresponding period of about four years.

Fatalities.—There were 3 patients who died before or just after diagnosis but one patient succumbed to a ruptured aneurysm on the posterior inferior cerebellar artery (though he had an angioma of the cerebellum in addition which might have been responsible for a previous hæmorrhage) and another from a pulmonary embolus. Again 1 of the 3 late fatalities died from otogenic meningitis. In effect only 3 of the untreated patients had a fatal hæmorrhage from an angioma, death occurring five months, fourteen years and twenty years respectively after the onset of symptoms.

The Outcome in Relation to the Main Presenting Symptoms

A. Hæmorrhage.—21 of the 31 patients in this group who were followed up after diagnosis had one or more hæmorrhages previously. 12 had only a single hæmorrhage, 6 two hæmorrhages, at an average interval of three and a half years, 2 had three (at intervals of six, three, five and two years respectively), and one patient had four separate hæmorrhages before the diagnosis was established. Subsequently 5 of the 21 patients had further bleeds (one patient dying from this cause two months after the initial hæmorrhage) though the remaining 16 had no further trouble over a period averaging five years and exceeding eight in 4 instances. One of the 16 became hemiplegic before diagnosis and was still similarly handicapped four years after his last hæmorrhage and another who also had long standing epilepsy slowly declined to die seven years later from meningitis. The remaining 14 patients, however, were well at the end of the follow-up period and had no serious disabilities.

It might be expected that those patients who initially have multiple hæmorrhages would be likely to experience further trouble of this kind subsequently but the follow-up results do not support this supposition. One of the 2 patients who had three hæmorrhages before diagnosis had no further episodes in the next eight years, and the patient who presented with four separate hæmorrhages (which he had experienced at intervals of six, two and one year respectively) had no further trouble in the next ten years during which time he enlisted in the Army.

B. Epilepsy.—Although 13 of the 42 untreated patients were known to have had epileptic fits before diagnosis, only 8 were followed up for periods ranging between six months and seven years and averaging just over three years. In general the frequency of seizures did not change appreciably over this time and as only 2 of the 8 had more than occasional fits of a focal or generalized type before diagnosis, the symptom did not become disabling. One of the 2 patients, however, who had frequent seizures for eleven years before diagnosis, became progressively demented before he died from meningitis seven years afterwards. The other had focal sensory attacks on most days for at least thirty years before diagnosis and continued to have them with the same frequency over the next three years though,

despite his reluctance to take anti-convulsants regularly, he only had two attacks which were accompanied by loss of consciousness.

C. Migrainous headaches.—5 of the 6 patients who had experienced this symptom before diagnosis were followed up subsequently. 2 of them, with histories of fourteen and six years' duration ceased to be troubled by headaches in the next three years. Two further patients noticed a definite decline in the frequency and severity of the complaint.

It is evident that the follow-up of the untreated cases in this series does not contribute substantially to our knowledge of what might be termed the natural history of intracranial angiomas, largely because insufficient time has passed since these patients came to be diagnosed, yet it is worthy of note that few of them were severely incapacitated even after many years. Though angiomas may by rupture lead to death or permanent incapacity, it is evident that they are much less likely to do so than intracranial aneurysms. Olivecrona and Riives (1948) state that "in the end probably most, if not all, patients die of hæmorrhage or are completely incapacitated," but it is felt that this gloomy view of the natural outcome is not justified. Recently Potter (1955) has published figures supporting our view; 27 per cent of his patients survived for more than twenty years after the onset of symptoms and more than half of them had only slight disability, or none at all, at the end of this period.

The Results of Operative Excision

Under this heading are included several patients who harboured very small angiomas which had, nevertheless, produced either large intracerebral hæmorrhages or, in one case, a very large number of repeated proven subarachnoid hæmorrhages. Several of these patients had the lesion "obliterated" rather than excised, for after several clips had been applied to the abnormal vessels the lesion virtually disappeared and was further destroyed by diathermy. These cases are therefore counted as total excisions. 3 patients were believed to have had a total excision but in 2 a subsequent angiogram showed that a part of the lesion remained. In the remaining case, although total excision had apparently been achieved, the patient died two years later and at post-mortem was found to have sustained an intracerebral hæmorrhage at the site of the original angioma. No trace of angioma was discovered but it must be assumed that some small part had been left behind which had been obliterated by the terminal hæmorrhage. Taking in these cases of "obliteration" and of the three subsequently shown to have been incomplete extirpations there are 36 patients who have been treated by the method of excision.

One patient died post-operatively from a large extradural hæmorrhage which developed very rapidly later. There were two later deaths, one

from intracerebral hæmorrhage and presumably due to a remnant of angioma having been overlooked (*see* above). The other late death occurred in a patient who was rendered hemiplegic and aphasic by a large intracerebral hæmorrhage from a left frontoparietal angioma. In spite of excision of clot and angioma no improvement took place in her physical state. Her death ensued elsewhere over a year later. One further case was lost in follow-up leaving 32 patients for assessment of results (*see* Table XI).

TABLE XI

Gross operative results in 36 cases

Available for follow-up	32
Post-operative death	1
Late death	2
Lost in follow-up	1
	36

Period of follow-up since operation.—Excluding the 1 post-operative death, the 2 late deaths and the 1 patient lost in follow-up, the 32 remaining patients have been followed for the periods shown below:

0 to one year; 2, one-two years; 6, two-three years; 8, three-four years; 11, four-five years; and 5 for more than five years.

Working capacity.—29 patients are alive and doing full time work in their original jobs, as housewives or as school children. 3 are incapacitated. Of these 29, 9 show abnormal neurological signs but they are minimal save in 1 case. This patient has an expressive dysphasia and a moderate right hemiparesis yet she is fully employed as a music teacher to children.

Epilepsy.—Of the original 36 patients 19 had suffered from epilepsy before operation and of these 1 was lost in follow-up, 1 died post-operatively and 1 died a late death from hæmorrhage. 16 remain therefore for assessment of whom 9 continue to suffer from fits, 5 are relieved and 2 have had but a single fit. Of the series of 29 at full work, 13 had epilepsy beforehand, 6 continue to have fits, 5 are relieved of fits and 2 have had but a single episode. About 44 per cent therefore are improved or relieved of their epilepsy, a figure more or less in keeping with the results of surgical excision of other epileptogenic lesions.

There were 17 patients subjected to surgery who did not suffer from epilepsy previously. 13 remained free from fits and 1 died after operation. 2 patients have had only one fit in a period of two to three years follow-up, and 1 patient has an occasional rare fit.

Migrainous headache.—In only 4 of the 36 patients was a history of migrainous headaches elicited and 1 of these died post-operatively. 2 of the remaining 3 have been completely free from headaches having hitherto experienced attacks for five and forty-five years. The other patient continues with his migrainous attacks quite unaltered by excision of his angioma.

Subarachnoid or intracerebral hæmorrhage.—25 of the 36 patients under consideration suffered one or more hæmorrhages from their lesion. Of these 1 died post-operatively and 1 a late death a year after operation. No patient who had bled before operation had a hæmorrhage subsequently but 1 of the 2 patients dying a late death did so because of an intracerebral hæmorrhage from a presumed remnant of the angioma excised at operation. This patient was operated upon because of epilepsy and an advancing motor and sensory hemiparesis. The result therefore of *total* excision of the angioma naturally precludes subsequent bleeding.

The Results of Craniotomy and Ligation of Cortical Vessels

In certain cases it has been found impossible to decide on the operability of an angioma without actually examining it at operation. 16 patients having such angiomas were subjected to exploratory operation and total excision was then thought undesirable either because the lesion was mainly subcortical or because its position made serious post-operative sequelæ highly probable. In these 16 patients a number of cortical arteries and veins were occluded with tantalum clips and/or diathermy and in 4 considerable shrinkage of the angioma was demonstrated in subsequent angiograms. It is interesting to note that no patient was made worse in any respect as a result of such ligation of surface feeding vessels and in some a degree of improvement followed.

Of the 16 subjected to operation 11 are working full time, 3 are incapacitated as they were before operation, 1 case has been operated upon too recently to assess the result and 1 has been lost sight of.

Effect upon seizures of cortical ligation.—12 of the 16 patients had suffered from epilepsy before operation and in 6 the frequency of attacks was markedly reduced. 1 patient only, who has been followed for three years after operation, has been completely relieved of the frequent focal attacks which she suffered for a year beforehand. 4 patients continue with their seizures unaltered and 1 has been lost sight of.

No patient in this group of 16 has developed epilepsy which was not present before surgical intervention.

Effects of ligation of cortical vessels upon hæmorrhage.—There were 6 patients of the 16 in this group, who had suffered one or more episodes of hæmorrhage before operation. In only 1 case out of these 6, all of whom have been followed for between three and four years, has there been recurrence of hæmorrhage. This patient has had two illnesses in the four-year period since operation which might well have been due to fresh hæmorrhage but on each occasion he made a good recovery.

Of the 16 patients 11 showed abnormal signs in the central nervous system at the time of admission to hospital and 1 of these has been lost sight of in follow-up. Of the remaining 10, 7 are unchanged in this respect

whilst 3 have shown quite definite diminution in the pre-existing abnormalities.

Effect of ligation of cortical vessels upon migrainous headaches.—Only 2 of the 16 patients have a history of such headaches, one for twenty-one years and the other for eight years. In neither case have they recurred in three and a half years and three years since the craniotomy.

Ligation of the Common Carotid Artery

4 patients only were subjected to this procedure alone one being in deep coma due to sudden intracerebral and subarachnoid hæmorrhage twenty-four hours previously. A large thalamic angioma was revealed by angiography and ligation of the appropriate common carotid artery seemed the only measure possible. This patient continued his pre-operative downhill course and died twenty-four hours later. Two more patients were apparently quite unaffected by the carotid ligation and remained with signs and symptoms unaltered. One patient seemed to derive relief from pre-existing headache for a few months but in her case the parieto-occipital angioma was accompanied by an aneurysm of the internal carotid artery on the same side lying within the cavernous sinus; the amelioration of headache was most probably due to the effect of ligation upon the aneurysm. One year later the patient's symptoms and signs were unquestionably worse.

Exploratory Craniotomy

7 patients were subjected to this procedure alone but in only 2 of them was the presence of an angioma known before operation. In neither case was any form of vessel ligation thought to be indicated or possible. The other 5 patients were operated upon before angiography had become a generally applied mode of investigation and when the nature of the lesion was exposed by craniotomy the wounds were immediately closed. 4 of these 5 patients were subsequently treated by irradiation. 2 of these 4 died later, 1 in status epilepticus after a long progressive illness of twenty-one years' duration, the other originally diagnosed by a right occipital bruit with appropriate calcification in skull radiograms in 1938 at the age of 16 years died twelve years later very suddenly. From the description given by the parents this death was almost certainly due to a sudden intracranial hæmorrhage.

Effects of Deep X-ray Therapy

11 patients have received courses of deep X-ray therapy for their known and localized angiomas. In not one of these has there been any evidence of permanent benefit accruing from treatment. There are notes in several of the case records that the patient felt better for a few months or so but there has not been a single case in which pre-existing neurological

signs improved or in which epilepsy has been relieved or eliminated. Of the 11, 4 have since died, eleven, six, four and two months from the time the diagnosis was established. All 4 deaths were due to one or more subsequent hæmorrhages. 3 of the 11 are worse as regards signs and symptoms, 1 at seven years and 2 at four years from the time of treatment. The remaining 4 patients are still alive having shown no real deterioration for periods of fourteen, eight, six and four years respectively. Thus of these patients treated by irradiation over a third have died as a direct result of rupture of the angioma and of the remainder about half have become incapacitated with the passage of years.

It would appear from this small series of cases that irradiation is of little benefit in the treatment of intracranial angiomas, though Potter (1955) has recently pleaded for its reconsideration. 10 patients in his series received radiotherapy; only 1 patient died and 4 of the 10 survived for more than twenty years subsequently, half having only slight or no disability at the end of this time. In view of the small numbers of patients involved both in Potter's and the present series, they cannot be regarded as comparable. Factors such as the site and size of the malformation will naturally influence the outcome.

Discussion

The Mode of Progression of Intracranial Angiomas

Although there is almost unanimous agreement that intracranial angiomas are vascular anomalies and not neoplasms, there is abundant evidence to suggest that many of these malformations increase in bulk with the passage of time. This is probably due largely to the effects of repeated and often comparatively "silent" hæmorrhage though the vessels comprising and feeding the arterio-venous shunt increase in size in addition. Of more practical importance is the pathogenesis of the clinical manifestations. As has been seen these are occasionally slowly progressive from the onset, though more frequently they initially take the form of intermittent episodes with long periods of complete remission. Sooner or later, however, some degree of permanent disability which is apt to become progressive over months or years seems to result. Olivecrona and Riives (1948) considered that an important cause of this deterioration is that regions of the brain not directly involved by the angioma may be starved of blood by reason of the rapid shunt from the arterial to the venous side of the malformation. Another mode of progression of equal importance is illustrated by the following cases included in this series. Briefly it is suggested that rupture of one of the vessels comprising the angioma produces a small area of hæmorrhagic degeneration in the adjacent brain tissue. As the blood clot is absorbed together with the necrotic brain tissue, support to the walls of the angiomatous vessels is diminished, permitting further rupture—this time of greater

degree. A larger blood clot which sometimes becomes organized at the periphery is thus formed. The central liquid or solid clot may or may not be absorbed but in either case a secondary rupture of the angioma into this encapsulated mass will produce a large aneurysmal sac (a "false aneurysm") thus considerably increasing the total size of the malformation. At such a stage in its life-history the angioma has become space-occupying and may, if large enough, and in the appropriate situation, result in ventricular obstruction and set in motion a new chain of events which terminates in intracranial hypertension with its own attendant symptomatology. A very small initial lesion may in this way become converted into a very large and dangerous one. Each stage in the extension of the process is illustrated in the following case histories.

H. B.—S., a married woman of 36 was admitted for investigation on account of a proven subarachnoid hæmorrhage six months previously with loss of consciousness for six hours. At that time there were no localizing signs of neurological damage and she made an apparently perfect recovery. Two months later and four months before admission she had a major convulsion and rapidly passed into status epilepticus. After appropriate treatment she regained consciousness in twelve hours and again showed no evidence of permanent local damage. On admission the patient was entirely normal, neurological examination was negative and only an angiogram revealed the small causal lesion, an angioma overlying the superior frontal convolution on the right side measuring but 1 cm. in diameter. At operation the angioma was exposed and, lying just lateral to it, was a small area of greenish discoloured cortex about 1 cm. square. This abnormal cortex showed a small area of cystic degeneration and was totally excised together with the angioma. Recovery was complete and without sequelæ three and a half years later.

This is an example of the first stage of extension of a minute congenital lesion. The initial subarachnoid hæmorrhage may have left no permanent evidence of the vessels having ruptured but the attack of status epilepticus probably resulted from a small intracranial bleed, the relic of which was visible as a patch of discoloured cortex showing cyst formation.

The first intracerebral hæmorrhage may be much larger than in the above instance and it may in virtue of its site produce some evidence of local damage.

The parents of S. C. their 13-year-old daughter, were awakened early one morning by her screams and found her unable to move her left arm. On admission to hospital six days later she was markedly drowsy and had a complete left sided flaccid paralysis, a left cortical hemianæsthesia with associated loss of pain and touch sensation and a left homonymous hemianopia. Angiography (Fig. 1) revealed a very small angioma situated in the right parietal lobe. At operation on the seventh day after the onset of symptoms an enormous fusiform intracerebral clot in the white matter of the hemisphere was exposed and evacuated. It measured 10 cm. in its long diameter. The tiny causative angioma was identified and obliterated. Recovery was rapid; her drowsiness and hemianopia disappeared but the severe cortical sensory loss and the left hemiparesis persisted. A year later there was little weakness of the affected limbs but the cortical sensory loss remained severe.

Intracerebral hæmorrhage from an angioma is not always a dramatic event for the bleeding may be slow and produce steadily progressive signs leading to confusion in diagnosis.

E. P.—B., a left handed girl of 18, while under treatment for thyrotoxicosis, developed a severe right frontal headache and a mild nominal aphasia. The following day the headache persisted, the speech defect became more marked and the patient was drowsy. By the third day she had a left homonymous hemianopia, unequal pupils, the right being smaller that the left, bilateral ptosis, left lower facial weakness and slight pyramidal signs in the left arm and leg. On the ninth day her drowsiness abated and the headache disappeared. She had now developed papillœdema with hæmorrhages and the diagnoses considered at this time were cerebral thrombophlebitis, cerebral abscess or a degenerating glioma. On the eighteenth day a surgical opinion was requested and ventriculography was performed. In attempting to needle the right lateral ventricle a cyst was encountered from which 5 c.c. of fluid black blood were obtained. Two days later angiography revealed a small right parietal angioma measuring 1cm. in diameter. At operation, on the twenty-eighth day after the onset, the angioma was exposed and excised whilst a large clot, which was some 7-8 cm. in length and extending deeply, forwards and downwards into the posterior temporal region, was evacuated. When the clot was removed a very thin layer of brownish green brain tissue remained which was presumably the beginning of an attempt at capsule formation. The only residual sign in this patient after three years is a left homonymous hemianopia.

In this case the large space-occupying clot in the temporo-parietal region was thought from the progressive nature of the clinical story to have been due to steady hæmorrhage over a period of time and not to a sudden severe bleed. Encapsulation was minimal at four weeks from the onset and there was no sign of absorption of the clot. That this latter process can sometimes take place is illustrated by the following case record, although it left in its wake a highly dangerous lesion in the brain.

I. C., a 31-year-old woman, was admitted for investigation after recovering completely from two subarachnoid hæmorrhages. The initial bleed, which had taken place five months previously, produced unconsciousness with a subsequent amnesia of three weeks' duration, though focal neurological signs disappeared in a week. Twelve days later increasing pain in the back and neck rigidity was thought to be due to a further smaller bleed. At the time of admission she showed no neurological signs and was without complaint, but an angiogram showed a small angioma lying deeply in the left frontal region 3 cm. in front of the coronal plane. At operation greenish broadened convolutions were exposed in the left frontal region deep to which a large, smooth walled cyst containing faintly yellow fluid was encountered. This cyst was lined by faintly brownish brain tissue but it had no firm capsule and was separated from the anterior horn of the ventricle by a thin translucent membrane only. The angioma lay in the superior surface of the cyst and was easily removed. Recovery was uneventful and there were no sequelæ or complaints two and a half years later.

If a further rupture of the angioma had taken place the hæmorrhage would almost inevitably have penetrated the thin membrane into the

ventricle and would possibly have led to the death of the patient. This patient had apparently achieved complete absorption of a large hæmorrhage leaving only a thin-walled cyst as evidence. Nevertheless firm encapsulation can take place as is well shown by the next case history.

I. P., a married woman of 33, suddenly went into coma when thirty-two weeks pregnant. Lumbar puncture demonstrated the presence of subarachnoid hæmorrhage. Some recovery took place but she was severely hemiplegic on the right and very aphasic when she was delivered five weeks later. Two weeks afterwards a further episode occurred associated with right sided convulsive attacks. On her admission seven weeks after the original bleed she was very lethargic and could just obey simple commands. She had a complete spastic right hemiplegia, a total expressive aphasia and a right homonymous hemianopia. Sensory testing was impossible. Angiograms revealed a fairly large angioma lying high up in the anterior parietal region on the left side (Fig. 2).

Ventriculography showed dilatation of the whole of the right and of the anterior horn of the left lateral ventricles. There was a shift of the system to the right side and a filling defect in the depressed left lateral ventricle (Fig. 3).

The diagnosis of a large, intracerebral clot associated with the angioma was obvious. At operation, fifty-nine days after the initial intra-cerebral and subarachnoid bleeding, a high left parietal bone flap was turned exposing the angioma. An incision through the cortex anteriorly encountered a firm capsule ½ to 1 cm. in thickness which readily dissected out from the adjacent brain much as would a cystic secondary carcinoma. Within the capsule was fairly firm black blood clot. The angioma was subsequently removed. There was no communication between the encysted hæmorrhage and the ventricle. No improvement in the patient's condition accrued from operation and six weeks later she was returned to the admitting hospital still totally aphasic and hemiplegic.

Here, two months after the first hæmorrhage, good encapsulation of the clot had occurred and the way was paved for a subsequent rupture of the angioma into a preformed cyst. That such a secondary rupture into an existing encapsulated hæmorrhage can take place is suggested by the following case.

A. D., a young man of 28, was originally admitted under the care of one of us in 1947. Ten years previously when 18 he had developed over a period of a few hours a left hemiplegia, beginning in the hand and later involving the leg and face. For three days he suffered severe headache. During the next six weeks most of his signs disappeared and he was left with only slight weakness of the left leg. When 26 he had the first of six major epileptic attacks. On admission for investigation of his epilepsy he showed only mild hemiparesis. There was a systolic bruit audible over the right frontal region. Radiograms of the skull showed an incomplete ring of calicfication high in the right frontal region measuring 5 cm. in diameter (Fig. 4).

An angiogram at that time (1947), showed a large multiloculated aneurysmal sac fed by an artery two-thirds of a centimetre in diameter running into it from above and in front (Fig. 5).

Other abnormal vascular channels were seen running up from the middle

cerebral artery. At the time the condition was felt to be inoperable and the patient was sent home with symptomatic treatment for his epilepsy. Two years later the patient was readmitted on account of the occurrence of two major epileptic attacks in the preceding week each having commenced focally in the left arm. Examination then showed that he had a complete left foot drop with spasticity of the whole left lower limb and weakness at knee and hip. There was wasting of the limb and some impairment of all forms of sensation. No bruit could be detected in the right frontal region on this occasion. Angiograms confirmed the original findings of a very large angioma but the aneurysmal sac had now been partly occluded by extensive clot formation (Figs. 6 and 7).

In view of the steady progression of physical signs in the left lower limb and the continuance of epilepsy in spite of anti-convulsants, operation was deemed the best course to pursue. A large right fronto-parietal flap was turned and a most extensive angioma overlying the aneurysmal sac was exposed. Total excision was achieved, the main artery being controlled and divided first and the main exit vein, measuring 1 cm. in diameter and running into the superior longitudinal sinus, last. Recovery was good. Four and a half years afterwards he had slightly less in the way of neurological signs than before operation and had not suffered a single fit.

Here then the story is that of a sudden intracerebral hæmorrhage with a hemiplegia which largely recovered in the following months. Ten years later a calcified capsule is present and the fistulous communication with the angioma is revealed by angiography. The deterioration in his physical signs over the ensuing two years indicated the progressive nature of the lesion up to the time of total excision of the angiomatous mass.

The mere presence of such a large space occupying lesion in certain regions of the brain may, as in the case of an intracranial tumour, lead to progressive symptoms with rising intracranial tension.

S. O., a shoe repairer of 59 years, was admitted on account of a two-month history of failing vision, falling attacks and progressive clumsiness in the use of the left arm. His previous history showed that he had suffered from migraine with teichopsia for forty-five years and epilepsy, commencing with a visual aura leading to unconsciousness and incontinence, for forty-three years. Seventeen years previously he had a sudden episode of severe headache and vomiting followed by neck stiffness. He was diagnosed as having sustained a subarachnoid hæmorrhage but we have no information regarding his physical signs at that time. On admission he was found to have a considerable memory defect, bilateral papillœdema, rather poor visual acuity (V.A.R. 6/18, V.A.L. 6/12 with correction), a small right pupil and a mild left hemiparesis with unsteadiness of gait. Radiograms of the skull showed evidence of prolonged rise of intracranial pressure, shift of the calcified pineal body 1 cm. to the left and calcification, with one ring-like shadow lying behind and below the pineal about 3 to 4 cm. from the mid-line. Angiography confirmed the presence of an occipital angioma but showed no contrast in the region of the deep ring of calcification. A very large angioma was excised on the deep surface of which was a smooth aneurysmal mass which had been compressing the trigone of the right lateral ventricle. Its cavity was completely filled with old organized clot and it had no internal circulation. The solid mass measured 8 by 6 cm. Recovery was rapid and three and a half years later the patient's only physical sign was a left homonymous

hemianopia. His headache and migraine have not recurred but he has had 8 epileptic seizures of the same type as those he suffered for forty-three years before operation.

This case also exemplifies the very long life history of some angiomas. Presumably the aneurysmal mass was born at the time of the subarachnoid bleeding. That it once formed part of the angiomatous circulation is shown by the laminated clot contained within it but it was later excluded from the abnormal vascular flow by total occlusion by clot. Eventually, as a space-occupying lesion, it interfered with the cerebrospinal fluid circulation and initiated the vicious circle of raised intracranial pressure which would have ended the patient's existence had it not been removed.

By their proximity to the third ventricle and the aqueduct of Sylvius, the central angiomas are likely to cause some degree of ventricular obstruction. Although only 2 of the 9 patients in this series were subjected to ventriculography the lateral and third ventricles were found to be quite markedly dilated in both instances (Figs. 8 and 9).

The intra- and para-ventricular angiomas furthermore may through repeated hæmorrhage into the ventricular system result in progressive internal hydrocephalus either by obstruction from arachnoiditis around the exit foramina or by recurrent clot formation within the ventricles themselves (Figs. 10 and 11).

Yet another cause of progressive symptoms is the formation of a subdural hæmatoma in association with hæmorrhage from an angioma. It will be recalled that 3 of the patients in this series had this complication which, though well recognized as occurring with intracranial aneurysms, has been but rarely reported hitherto. Clarke and Walton (1953) described a fatal case in which a large subdural hæmatoma had developed after rupture of a fronto-temporal angioma but they were only able to find three similar examples in the literature. Nevertheless this complication is clearly of importance.

The Diagnostic Value of Angiography

The value of angiography in the diagnosis of intracranial angioma is seemingly self-evident. 103 of the patients in our series were submitted to angiography and in every instance the diagnosis was confirmed by this procedure. We know of 2 patients, however, not included in this series, in whom the angiograms failed to demonstrate lesions which were subsequently shown by histological examination to be angiomas.

P. H., a boy of 14 was admitted to hospital for investigation of seizures of six years' duration with, latterly, marked changes in personality and behaviour. It is of note that the initial major seizure was followed by a transient right hemiparesis accompanied by aphasia. He was an aggresive, destructive and unco-operative youth. No intracranial bruit was heard but his right leg was slightly smaller than its fellow. Repeated Electro-encephalographic studies suggested an abnormality in the left frontal region, but his skull radiograms and lumbar air encephalogram were normal as also were left carotid angiograms.

A left frontal lobectomy was performed and at operation an oval area of brownish discoloration approximately 5 cm. in diameter was seen on the convexity of that lobe. Sectioning disclosed the presence of several collections of altered blood bounded by dense membranes, reaching medially to within a few millimetres of the anterior horn of the left lateral ventricle. Histological examination of the interstitial substance in the lesion showed that it was largely composed of gliosed cerebral tissue containing numerous small arterioles and capillaries as well as several larger vessels with thick fibrosed walls which had become occluded by connective tissue. The lesion was considered to be an angiomatous malformation.

H. S., a housewife who started having fits at the age of 27, was investigated in hospital on several occasions before she was operated on at the age of 38. By this time her personality and behaviour had deteriorated markedly while her seizures which were of a "temporal lobe" type were poorly controlled by anticonvulsants. No neurological abnormalities were found on examination although radiograms showed a ring of calcification in the region of the left temporal lobe and her electro-encephalograms indicated a left fronto-temporal abnormality. A left carotid angiogram was normal but a ventriculogram demonstrated slight elevation and lateral displacement of the temporal horn of the left lateral ventricle. At operation the under surface of the left inferior temporal convolution was seen to be discolored and on incising this region fresh black blood clot and necrotic brain tissue was extruded. Eventually a vascular mass some 6 x 5 x 4 cm. was cleanly shelled out of the temporal lobe. This mass was seen on sectioning to be partly vascular but the procedure was somewhat difficult as there was a considerable amount of hard calcareous matter at its periphery. Histological examination showed that the saccules were composed of enormous dilated blood vessels with fibrosed walls. In addition numerous small intercommunicating vascular channels were found in the interstices, which were bounded by fibrous tissue and lined by flattened endothelium. The lesion was thought to be an angiomatous malformation.

It is evident that in both cases the angioma contained vessels of sufficient calibre to have made them easily visible in angiograms had they not been excluded from the general circulation. The purely telangiectatic type of angiomatous malformation being composed of capillary and pre-capillary sized vessels will clearly be invisible in angiograms, though transitional forms in which part of the malformation is composed of much larger vessels are also found. These telangiectatic malformations can produce clinical symptoms in much the same way as the commoner arterio-venous types, but as they are usually situated in the brain-stem (Teilmann, 1953) though even there they are uncommon lesions, the fact that they may not show up in angiograms is perhaps of little practical importance.

Angiomas as a Cause of Subarachnoid Hæmorrhage

42 per cent of patients in this series had as their initial symptom a cerebral hæmorrhage which in the majority of instances leaked into the subarachnoid spaces and gave rise to the typical symptoms and signs of subarachnoid hæmorrhage (Table IV). Since the series was closed a further 50 cerebral angiomas have been encountered in the neurosurgical department of St. George's Hospital and 62 per cent presented initially

with a subarachnoid hæmorrhage. This increase from 42 per cent to 62 per cent is probably attributable to the growing number of patients who having sustained a subarachnoid hæmorrhage are referred directly to a neurosurgeon for investigation, for whereas 119 patients with subarachnoid hæmorrhages were investigated in the same department in 1953, 188 were seen in 1954. Of the total of 307 who presented in this way in these two years 58 per cent were found to have intracranial aneurysms and 12 per cent angiomas, so that the former were apparently five times as common a cause of subarachnoid hæmorrhage. This statement may well require modification for it will be seen that in nearly a third of the total no cause for the hæmorrhage was found, though it should be emphasized that most of the latter patients for various reasons were not submitted to vertebral as well as bilateral carotid angiography.

Methods of treatment.—The ideal form of treatment for an intracranial angioma is undoubtedly that of total excision and great credit is due to Olivecrona and Norlen for establishing the practicability of the method in quite a high proportion of cases. Unfortunately there are many angiomas which are not amenable to surgical extirpation by reason of their extent, depth or situation in the vital centres of basal ganglia or brain-stem. Yet nearly one-third of the patients in this present series were so treated. In some cases it may be necessary to proceed to exploratory craniotomy before making a decision as to the practicability of total excision. Having on such an occasion decided against an attempt at extirpation, the question of ligation of cortical feeding vessels naturally arises. Olivecrona has condemned the method as being valueless and indeed dangerous but we have employed it in some 16 cases with at least a modicum of success. Ligation of entering vessels cannot be expected to produce very much effect upon the really extensive angioma for so many of their feeding vessels enter from the deep surface. In some of the smaller ones, however, particularly where the motor or sensory cortex or the speech areas of the dominant hemisphere are involved and serious sequelæ would accrue from total excision, cortical ligation of entering vessels may be found to have a useful place in treatment.

Ligation of the common or internal carotid artery does not appear to be of any value in treatment. When one considers how many angiomas fill well where angiography is carried out on the side opposite to the lesion it is not to be expected that any real diminution in size would follow such an arterial ligature. As has been seen this method has rarely been used in this series and no improvement resulted.

Radiotherapy was extensively used in the past for, in some of the earlier cases in this series and especially in those where the lesion was exposed at exploratory craniotomy in the pre-angiographic era, irradiation was subsequently given routinely. Later still, after angiography had been well established but before surgical excision had been shown to be practicable,

several cases were similarly treated, but our experiences of the results of this form of treatment are, to say the least, disappointing.

Addendum

23 of the additional 50 angiomas encountered since December 1952, were excised with only one death. This occurred in a patient who had a large intraventricular angioma which had caused serious disability before operation was attempted. Death took place two months later from pneumonia. As three other patients treated by excision had intraventricular angiomas, it will be seen that the latter constituted some 8 per cent of these additional 50 examples, a proportion which is much higher than that obtaining in the original series (*see* Table I). This rise is again probably due to the increasing number of patients entering a neurosurgical unit for investigation of a subarachnoid hæmorrhage for it will be recalled that both of the 2 patients in the original series who had intraventricular angiomas presented in this way and had no localizing symptoms or signs.

Summary

The symptoms, signs and modes of presentation of 110 patients with intracranial angiomas are reported.

The cardiovascular effects, radiological features and associated complications of intracranial aneurysms and subdural hæmatomas are reviewed.

The situation and size of the malformation in relation to the symptomatology are discussed.

The mortality and subsequent progress of untreated cases in this series are detailed and the surgical measures employed together with their results are reviewed.

The modes of progression of these lesions are considered and exemplified by illustrative case records.

The diagnostic value of angiography is discussed and the frequency with which angiomas cause subarachnoid hæmorrhage is commented upon.

Possible methods of treatment are discussed and it is concluded that whenever possible total excision of the angioma is the ideal method of treatment. Ligation of cortical feeding vessels seems not to be without value in certain instances. No evidence is found to suggest that radiotherapy is of real value.

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LEGENDS FOR PLATES

PLATE VIII

FIG. 1.—Patient S. C. Right lateral angiogram showing small angioma which, in rupturing, produced a very large intracerebral hæmorrhage with resultant hemiplegia, hemianæsthesia and hemianopia.

PLATE IX

FIG. 2.—Patient I. P. (1) Lateral angiogram showing angioma with hypertrophied anterior cerebral artery supplying it.

FIG. 3.—Patient I. P. (2) A. P. anterio-posterior ventriculogram showing large left fronto-parietal space occupying lesion.

PLATE X

FIG. 4.—Patient A. D. Lateral radiogram showing calcified aneurysmal sac (1947).

FIG. 5.—Patient A. D. Right lateral angiogram revealing angioma and complete filling of the aneurysmal sac with dye (1947).

PLATE XI

FIGS. 6 and 7.—Patient A. D. A. P. and lateral angiograms two years later showing partial occlusion of aneurysmal sac by clot.

PLATE XII

FIGS. 8 and 9.—Lateral ventriculogram and Myodil ventriculogram showing ventricular dilatation and obstruction of posterior end of third ventricle by a thalamic angioma which had bled on several occasions.

PLATE XIII

FIGS. 10 and 11.—Lateral angiograms taken in 1949 and 1953 from the same patient showing increase in degree of hydrocephalus due to frequently repeated hæmorrhage from an angioma in the corpus callosum.

PLATE VIII

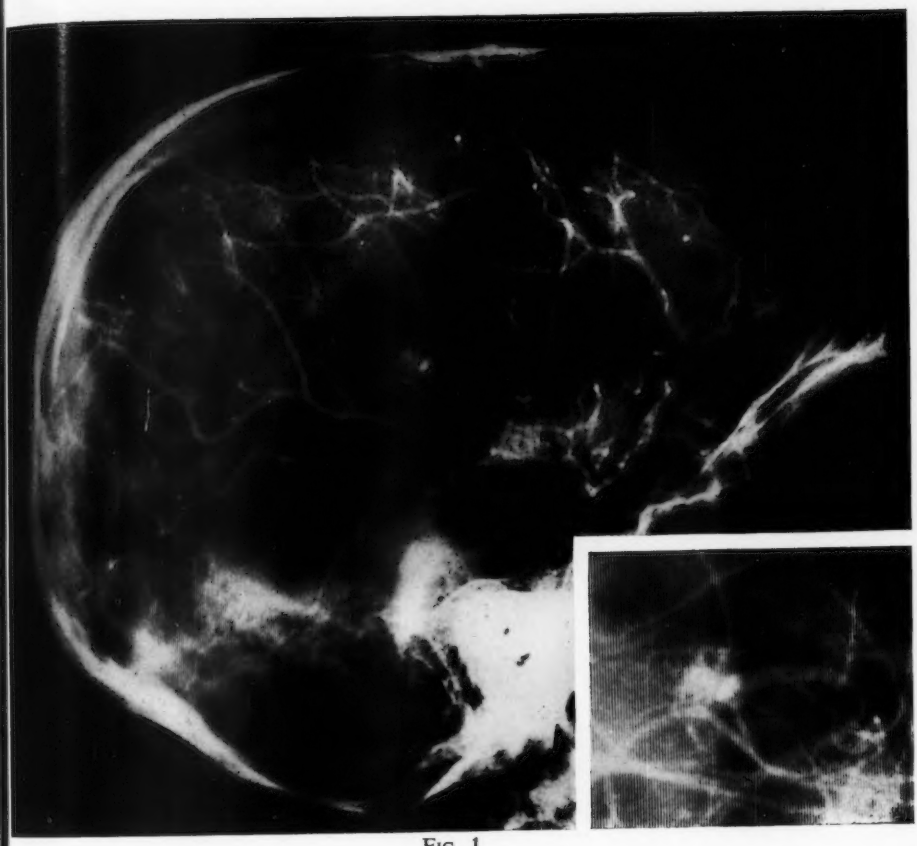

FIG. 1.

To illustrate article by J. Hamilton Paterson and Wylie McKissock.

PLATE IX

FIG. 2.

FIG. 3.

To illustrate article by J. Hamilton Paterson and Wylie McKissock.

PLATE X

FIG. 4.

FIG. 5.

To illustrate article by J. Hamilton Paterson and Wylie McKissock.

PLATE XI

FIG. 6.

FIG. 7.

To illustrate article by J. Hamilton Paterson and Wylie McKissock.

PLATE XII

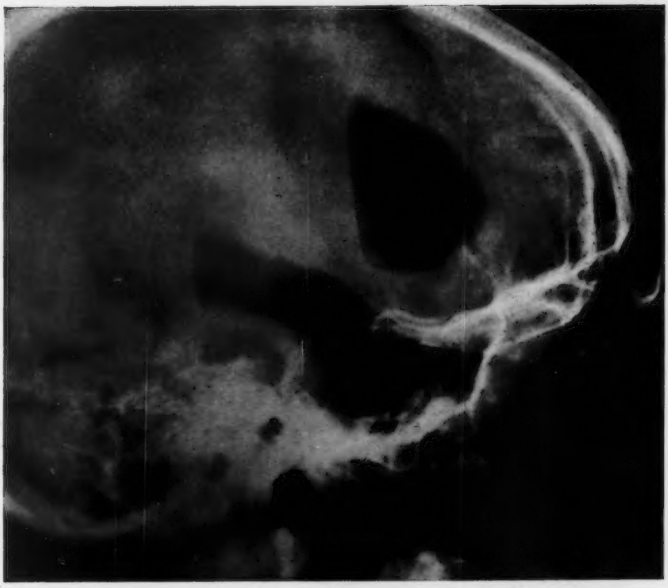

FIG. 8.

FIG. 9.

To illustrate article by J. Hamilton Paterson and Wylie McKissock.

PLATE XIII

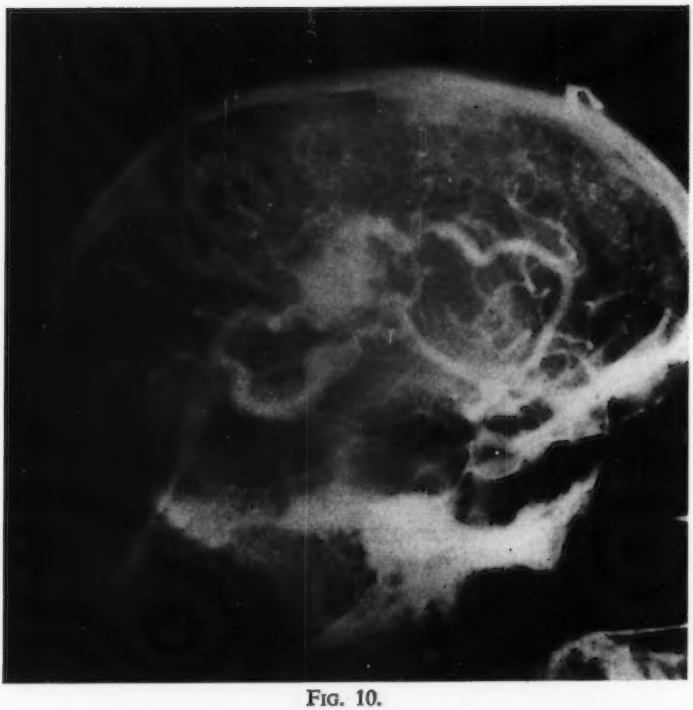

FIG. 10.

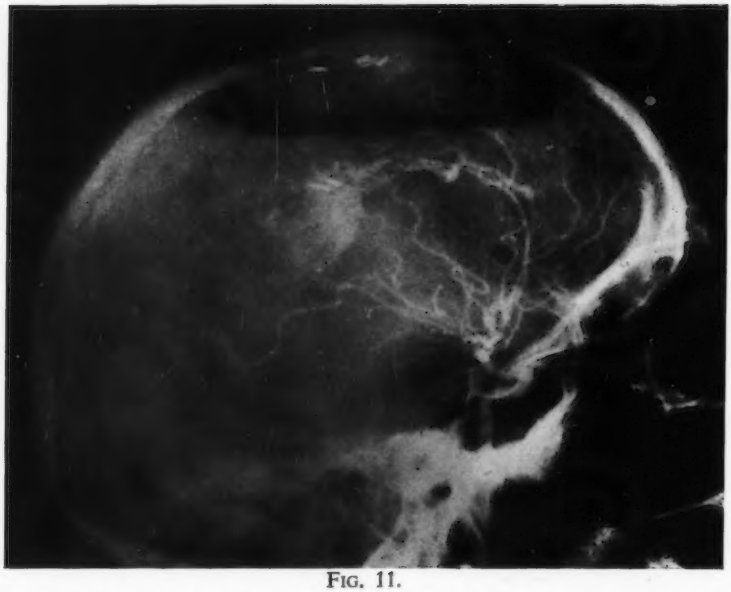

FIG. 11.

To illustrate article by J. Hamilton Paterson and Wylie McKissock.

THE EFFECT OF OLFACTORY STIMULI IN ARRESTING UNCINATE FITS

BY

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INTRODUCTION

DURING the aura of epilepsy or migraine, many patients report a compulsion to perform some act, which they feel may abort the full attack. Many of the bizarre rituals which have been developed are of no avail but some fortunate patients chance upon a "solution" to their problem which the physician may be unable to explain. A striking example is the well-known phenomenon of aborting a focal epileptic seizure by a powerful sensory stimulus such as the application of a tight ligature to the finger first affected, in the course of a Jacksonian fit. Since ancient times, the Jacksonian fit has also been arrested, with variable success, by other types of strong, unpleasant sensory stimuli; by the vigorous massage of the muscles of the hand or foot, by forcibly resisting the first tonic spasm, by plunging the whole extremity into ice water, by pricking it repeatedly with a pin, or by the application of the blister. Similarly, other fits are occasionally arrested by non-specific sensory stimuli.

Sir William Gowers in 1881 wrote: "Attacks which begin by a general or bilateral aura, or by the epigastric sensation, can rarely be arrested, but now and then they may be stopped by some muscular exertion, as by walking quickly about the room, or by a strong sensory impression, such as the application of ammonia to the nostrils, and sometimes by the inhalation of nitrite of amyl." He also wrote: "Attacks which begin by other warnings are sometimes arrested by other forms of peripheral sensory impression, by a strong gustatory sensation, as by chewing a piece of ginger, by a strong olfactory impression, as by the application of ammonia to the nostrils, or by swallowing a handful of common salt. More uniformly successful, however, is the inhalation of nitrite of amyl. If it produces a flushing of the face before the patient loses consciousness the attack is usually cut short. The cases in which I have found it most frequently successful have been those with a deliberate olfactory aura."

[1] The opinions expressed in this article are those of the author and are not necessarily to be construed as representing those of the Navy Department.

Most neurological texts tentatively accept Gowers' suggestion that this type of sensory stimulation usurps or renders temporarily refractory the central pathways to be used by the spread of the epileptic discharge, preventing the "march" and terminating the attack before a generalized seizure ensues.

Gowers' hypothesis was never subjected to investigation in either the clinic or the laboratory. Other experiments were performed in related areas: (1) Erickson (1940) recorded a Jacksonian march in an anæsthetized dog, and followed the spreading after-discharge with electrocorticograms. He proved that the march is largely a cortical phenomenon and is independent of deeper white or grey matter. He demonstrated by means of a cortical incision at right angles to the spread, that the march was blocked at that point, resulting in a complex detour of the march via the corpus callosum to the contralateral side. (2) McCulloch (1949) reported *acceleration* of the spread of the surface-negative wave of after-discharge when dilute solutions of strychnine were applied to the cortex in the path of the oncoming wave and assumed from this that the spread was mediated by a transneuronal activation rather than by the release of a metabolite. (3) Many studies have been performed (Amantea, François-Franck, Gellhorn and others) using different methods of inducing generalized or focal seizures with sensory stimuli. Forster and Madow (1949) showed that in normal animals, it was necessary to place acetylcholine on the cortex in a given area (auditory cortex) and then to administer parenteral metrazol, before a series of clicks induced a spreading after-discharge from the auditory area. An acetylcholine-treated cortex responded only with a localized after-discharge when the clicks were given—metrazol was necessary to produce a widespread activation. (4) Leão (1947, 1948, 1949) discovered a "spreading depression" in the cortex and produced this depression in three ways; by brief, subthreshold electrical stimuli applied to the pial surface, by a mechanical irritation of the pia or cortex, and by application of dilute solutions of potassium chloride. He found that all electrical activity of the cortex—whether spontaneous or induced—could be blocked by his "spreading depression" which was always associated with profound, visible, vascular changes of the pia. (5) Gellhorn (1947, 1948) showed that nociceptive afferent impulses (produced by electrical or mechanical stimulation of the sciatic nerve, or by intramuscular injection of hypertonic saline) caused spiking activity in the "suppressor" areas of the cortex (as defined by Dusser de Barenne, McCulloch, and Garol) as well as in the primary somesthetic areas for the particular region so stimulated. A rather powerful stimulus was used—one which in an unanæsthetized animal would have produced excruciating pain. He did not attempt to correlate the degree or the extent of cortical localization of this activation with varying intensities of pain. Experiments of this type have not been performed with unpleasant (nociceptive)

olfactory stimuli in either animals or man. (6) Francois-Franck (1887) recorded his failure to abort focal Jacksonian fits, induced in anæsthetized dogs by local faradization, by violent nociceptive stimuli such as squeezing the testicles, or twisting the digits forcefully. He did not, however, mention the time relationships between these peripheral stimuli and the faradization of the cortex.

That no laboratory studies have appeared on the inhibiting effect on the *march* by a purely sensory stimulus despite Gowers' important clinical observations and the conventional acceptance of his theories is odd. That his observations on the olfactory stimulus in particular have been totally disregarded is more understandable due in part to his dominant use of amyl nitrite. The use of this chemical, which produces such profound changes in vasomotor tone and cerebral blood flow, introduced so many physiological side reactions as to obscure its specific olfactory role. Indeed, Gowers himself was of the opinion that,

> "it is scarcely conceivable that the effect of amyl is produced through the olfactory nerve. Its influence may be held to afford some support to the doctrine that the sudden contraction of the cerebral vessels is the essential element in the attack."

There is another, and perhaps more profound, cause for the neglect of Gowers' observations. Neurologists have been understandably sceptical of all attempts, most of them derived from folklore, to abort seizures with sensory stimuli. The isolated case reports of this phenomenon, and the review of the subject by Brown-Séquard (1857–1858) have made little or no impact, particularly since bromides and barbiturates have suppressed seizures more regularly—and with less apparent mystery. The author himself was only aware of the historical references to the effect of ligatures in aborting focal motor and sensory fits, and was surprised to find that his "original" discovery of the importance of the olfactory stimulus in arresting uncinate seizures, had been already discovered by Gowers more than seventy years ago. The experimental use of the olfactory stimulus in the therapy described in this case report was actually inspired by the unusually articulate and analytical description of a recurrent seizure pattern by an introspective patient. The intricate nature of the reported olfactory aura, and the patient's compulsive belief that any interruption of the inexorable step-wise march of the psychic aura would arrest the seizure, prompted this therapy.

CASE REPORT

Mrs. T. B. is a 41-year-old American negress, and a professional singer. Her maternal grandfather, first cousin, and daughter all suffered from "convulsions" or "fits," none of which were similar to hers. She had her first fit at the age of 15, and has continued to have an average of 7-18 a month, at irregular intervals of never less than two weeks in the past 26 years. Varying doses of phenobarbitol and diphenyl hydantoin did not alter the frequency or character of the attacks.

Eclampsia complicated her first pregnancy, and the patient's first uncinate fit occurred shortly after recovery. She has been chronically hypertensive since that time and had three subsequent episodes of eclampsia. Three of her six pregnancies miscarried. At 35 she developed a left sided hemiplegia lasting a few days, with complete recovery. This was followed, several months later, by a more profound left hemiplegia for which she was in hospital for a year. The cerebral thrombosis did not alter the frequency or character of her seizures.

Physical examination on 6-1-55 revealed an obese, alert woman with moderate spasticity on her left arm and leg, slight foot drop with a dragging gait and unsustained clonus of the ankle. The left arm was flexed at the elbow and the wrist. There was weakness of all movements of the arm and leg and an associated hyperactivity of the stretch reflexes on this side. There was hypæsthesia for all modalities of sensation on the left side including the face. The cranial nerves were otherwise normal and there was no facial weakness. Orientation, reasoning, speech and symbolic functions were grossly intact although careful psychological testing [1] did reveal mild evidence of organic deterioration consistent with the old cerebral thrombosis. The blood pressure was 160/90 and her retinal arterioles were narrow and tortuous. There were multiple scars and bruises in all regions resulting from her many fits, in addition to one scar on the tongue.

The patient, in describing her many seizures, stated, "They are all like cars coming off the assembly line. I can't tell one from the next." She denied any "mild" attacks or abortive forms and did not know what they were until described. She insisted that the particular sequence of psychic events, once established, was invariably followed by a seizure. She described that part of the attack of which she is conscious in these terms: "I can be perfectly well in every way when suddenly I feel snatched away. I seem to feel as if I'm in two places at once but in neither place at all—it is a feeling of being remote. I can read, write and talk and can even sing my lyrics. I know exactly what is going on but I somehow don't seem to be in my own skin. Sometimes it wakes me up at night, but it usually develops during the day. When this feeling happens I know that I'm going to have a convulsion. I keep trying to stop it from happening. No matter what I do, it always comes. Everything goes ahead like a railroad schedule. At this part of my attack I feel very active. If I'm home I make beds, dust, sweep or do the dishes. My sister says that I do everything at breakneck speed—I rush around like a chicken with his head cut off. But to me it all seems to be in slow motion. I am very interested in the time, I'm always looking at my watch and asking someone the time every few minutes. That is why I know exactly how long this part of the attack lasts. It has been as short as ten minutes or may last the better part of a day; it is real hell then. Usually it lasts about twenty to thirty minutes. All this time I feel that I'm remote. It is like being outside a room and looking in through a keyhole, or as if I'm God just looking down on the world but not belonging to it. This feeling gets slowly worse during this part of my attack."

On direct questioning the patient reported that she feels that her sense of smell is altered all this time. She has noticed that cooking smells seem just "slightly different" from usual, and that this is the case throughout the seizure period.

"After this has gone on for some time, I seem to get to what I call my 'half-way point.' I know just about when it is coming. When it happens I suddenly get snatched even further away. I am more remote than before. I still know exactly what is happening but now I don't give a damn. I'm no longer impatient. I

[1] Kindly performed by Miss E. King, Department of Neuropsychiatry.

don't care what happens. I feel like a piece of clay, inert. I don't try any more to prevent the convulsion."

"It is also at the half-way point that I get a funny idea in my head. It is hard to put into words. It is just that I expect to smell something any moment, but I don't yet. I don't think that this is due to my having had so many of these seizures. The first time it ever happened, I was out in the country and I was feeling funny. I was in a field picking forget-me-nots. I remember very well that I kept smelling these flowers even though I knew they had no odour. For about half an hour I kept sniffing them because I was sure they would begin to smell soon. I clearly remember telling this to my friend. I was somehow expecting them to smell even though I knew perfectly well at that time that forget-me-nots have no odour at all. When I'm getting this feeling of a smell coming I'm so far away from the world that I almost don't know I'm so remote, but yet a corner of my mind still knows I'm remote. I know it and don't know it at the same time. (The mental diplopia of Hughlings Jackson.) It is so intense that I don't seem to be aware of anything but this feeling of remoteness and the feeling that a smell is coming. This feeling gets worse and worse and I seem to be floating away. Yet I know what is happening all the time. I can read and talk but I don't feel like it. I used to read the Bible out loud at this stage but gave it up because my family couldn't stand the monotonous tone of my voice. They said I sounded like a funeral orator. So now I don't do that any more."

(On one occasion the patient called on the telephone during this phase of her attack. Her voice had lost its character and identifying marks and was not recognized. It had a monotonous, featureless, expressionless quality. The normal accentuation which in this woman has a characteristic American negro drawl, was absent.)

"The part of the attack from the half-way mark to the convulsion is always shorter than the first part. It may be only five minutes long but is never longer than twenty to thirty minutes. I'm no longer interested in the time. I used to keep on working even though I felt this way but I had so many knocks and bad falls that I began to lie down on the floor. I push all the furniture away so that I don't hurt myself when it happens. Then, just when I seem to be as remote as I possibly could get I suddenly get a smell like an explosion or a crash. There is no buildup (intensity). It is all there at once. At the same moment that the smell crashes through, I'm back in the real world—I no longer feel remote. The smell is a disgusting sweet, penetrating odour like very cheap perfume. I just stop still when I smell it. Everything seems very quiet. I don't know if I can hear. I am all alone with the smell. I don't think this lasts for more than a few seconds and then the smell rapidly goes away. Then I find myself almost normal except that it still seems very quiet. This quietness lasts about five to ten seconds but I'm really not sure. Then I hear a voice off to the right calling my name, "Thelma, Thelma." It keeps calling. This is not like hearing a voice in a dream. It is a *real* voice. Every time I hear it I fall for it. It is not a man's or a woman's voice. I don't recognize it. There is one thing that I do know and that is if I turn towards the voice I have a convulsion. I try hard not to look towards the voice. I have often turned my head to the left to keep from looking towards the right. But the voice keeps calling my name, almost as if it wants me to turn to it. No matter how hard I try I have never been able to keep from turning my head towards this voice. I always feel that if I didn't look I wouldn't have a convulsion. But it is irresistible. As my head turns, it seems to start slowly, then faster and faster. Finally there is a big jerk and my head swings around to the right. Sometimes I am barely aware that my right arm flies up. That's it. I'm out. I have the convulsion after that."

Her convulsions have a tonic and clonic phase. One attack witnessed and recorded electrically began with a tonic contraction of the arm and legs in the extended position with flexion of the trunk. Her head was turned sharply to the right and both eyes were deviated to the right. There were no preceding swallowing or lip smacking movements. This lasted for only four to five seconds and was followed by a clonic seizure lasting about one minute in which the movements were much more marked on the right than on the hemiplegic left side. She was incontinent. She was disoriented for about five minutes in the post-ictal period during which time she had a marked paraphasia.

CLINICAL STUDIES

It was tentatively assumed for the purposes of this study that the series of subjective events described by the patient reflected the spread of a wave of excitation over the surface of the left temporal lobe. If the theory of pathway usurpation is correct, it should be possible to arrest this patient's seizures by the application of a specific sensory stimulus at a critical time.

It seemed logical to introduce an extraneous, powerful odour, just before she reached the point when the olfactory hallucination occurred. The patient was provided with a vial containing n-ethyl butyrate—which produces a sharp, pungent and distinctly unpleasant odour—to be inhaled at this moment. This procedure was followed for three seizures and *failed* each time to abort the endogenous odour, the voice and the *grand mal* climax.

To understand this failure, it is important to analyse the patient's deepening anticipation of a smell. There are at least two possible explanations of this phenomenon. One might reasonably be that her feeling of anticipation is purely psychological—conditioned by many uncinate discharges—and unrelated to the fit *per se*. Another possibility is that this anticipation of a future odour represents a spread of the discharge to some "higher" olfactory centre but not yet to the primary smell receiving area. The anticipation would then represent a type of "forced thinking," characteristic of temporal lobe epilepsy and considered to be part of the ictal process. The patient's account of her first uncinate seizure—with the anticipation of smell—gives strong evidence against psychological conditioning. The second possibility—anticipation due to a "positive" epileptic effect—would suggest that the olfactory system was already involved in the epileptic disturbance at this stage. The failure of the n-ethyl butyrate might thus be due to its *delayed* use.

At this point in the experiment the patient made an irrelevant observation which is of interest because it caused a change in the chemical used as a stimulus—a change which will be shown to have no bearing on the problem. She stated that the n-ethyl butyrate was very similar to the endogenous odour, and wondered if she might be given an "opposite" odour to smell. Given a choice of chemicals, she decided that hydrogen

sulphide was the "opposite" smell and quite strong enough. She was provided with small bottles containing 5 cc. each of 20 per cent hydrochloric acid and many small pellets of ferrous sulphide. She was instructed to drop a few pellets into the acid when she wished to produce the odour, and was told to sniff it just *before* her "half-way point." She was provided with a number of bottles to be used when she felt her seizures developing. She was told not to use these vials unless she had an aura identical in every respect with those she had experienced for the previous twenty-six years. A brief abstract of the result of each of these vials follows:

Vial No. 1—*Failure.*—The patient tried to time the onset of the "half-way point" but it came upon her just before she was about to smell the hydrogen sulphide. The endogenous odour was delayed in its appearance, but when it did develop the seizure went forward unimpeded to its *grand mal* climax.

Vial No. 2—*Incomplete success*—She sniffed the gas at the "half-way point" and found herself involuntarily running in a circle about five feet in diameter, in a clock-wise direction—"turning the same way I would if I were looking at the voice." *The endogenous odour never appeared nor did the voice or the grand mal component.* She continued to run in a circle for about ten to fifteen minutes (by the clock) until she fell exhaused to the floor. She sat panting on the floor until she regained enough strength to get up. She then felt perfectly well, though fatigued, but was very anxious about this experience. She had never before experienced the aura of depersonalization without the full maturation of the seizure. She observed that her head felt full of "cotton" and that she was lightheaded. She remained in this state for another fifteen minutes and was then perfectly well.

She was markedly depressed at the result and felt that she would rather have a seizure than run in this fashion again. She had experienced this manifestation of epiplepsia cursiva only once previously—during the unsuccessful early trials of n-ethyl butyrate. The first episode—in which she ran purposelessly throughout the house until struck down by a fit—did not involve the circling movement.[1]

Vial No. 3—*Complete success*—Smelled hydrogen sulphide at the stage just prior to the "half-way point." She noted the gradual disappearance of the sense of remoteness and never reached the "half-way point." She had a lightheaded feeling for several hours after this inhalation but *did not develop the endogenous odour, the voice, the grand mal seizure, or any manifestation of epilepsia cursiva.*

Vial No. 4—*Continued success*—Smelled hydrogen sulphide at a stage just prior to "half-way point." The psychic manifestations of her dreamy state "went backwards." This was her first experience of a recession of the depersonalization. She felt very lightheaded, miserable and depressed. She was certain that something frightful would happen. She developed an acute anxiety state. A routine electro-encephalogram taken at this time was normal.

[1] It is interesting to note at this point that circling movements identical to this have been produced in animals by a variety of techniques. Essig, Hampson, McCauley, and Himwich (1950) produced this in a wide variety of species by intra-carotid injections of subconvulsive doses of di-isopropylfluorophosphate (DFP). The circling was in the direction opposite to the side of the injected carotid. Kennard and Ectors (1938) were able to produce similar behaviour by selective frontal lobe resections in dogs.

Vials Nos. 5 and 6—Continued success—Hydrogen sulphide inhaled very early in this aura. Recession of the depersonalization within two minutes. Symptoms of lightheadedness and "numbness" of the head as an aftermath. Several hours later another seizure began and this time the patient waited until just prior to the "half-way point." Inhalation of Vial No. 6 completely aborted the attack. The numbness of the head persisted for about five to six hours.

Vial No. 7—Continued success—Seizure again aborted. She felt quite ill and nauseous after smelling the hydrogen sulphide.

It is clear from the results of the first seven vials of hydrogen sulphide that astonishing success was achieved in aborting the patient's *grand mal* seizures by the use of an olfactory stimulus. A pertinent question can be raised at this point: Was the patient's response influenced to any significant extent by psychological factors of suggestion?

While one must assume that some degree of suggestion did take place (although there was no external evidence of this)—it cannot have played a determining or even significant role. Epilepsia cursiva—particularly of the circling type (a manifestation of temporal lobe epilepsy) had never existed previously in this patient—and she had no knowledge of it. Yet it appeared when the discharging pathways were apparently side-tracked by the olfactory stimulus administered at a critical point, in almost the same fashion that the march was detoured in Erickson's (1940) studies. This is impossible to explain on the basis of suggestion. Similarly, suggestion would hardly explain the patient's consistent failure to abort any one of her epileptic attacks when the inhalation occurred *after* the onset of the concept of impending smell, and here again she received no information concerning the hypothesis of this experiment from any source. It is also psychologically significant that despite the success in arresting her *grand mal* climax, at no time since the treatment was first started has the frequency of her seizures decreased.

A second pertinent question can be raised here: Was the success of the therapy due to the neurophysiological effect of the odour or to the pharmacological effect of hydrogen sulphide? Again, this was easily investigated: Hydrogen sulphide is known to produce a histotoxic anoxia. Indeed, the patient experienced headache, lightheadedness, and numbness of the head—symptoms of hydrogen sulphide poisoning. The patient was therefore given a new drug: BAL (dimercaprol), a material which has a smell similar to that of hydrogen sulphide, probably due in part to the SH molecular grouping. She inhaled this material in exactly the same fashion with equally successful results in aborting ten seizures. Brief descriptions of the results of the use of BAL leave no doubt that the success of hydrogen sulphide was not due to a histotoxic anoxia:

BAL Vial No. 1—Success—BAL produced immediate loss of symptoms of depersonalization. Felt completely well after five minutes. No sequels of headache, numbness, or lightheadedness. Seizure completely aborted.

BAL Vial No. 2—*Success*—Patient insisted that the seizure developing on this day began at the point where the one had been terminated the night previously. No explanation can be offered for this. Inhaled BAL and a complete lysis of the seizure occurred. She had not reached the "half-way point" when inhalation occurred. She reported that the BAL did not smell as it did in the inter-ictal period, even at this early stage of her aura. (This agrees with her previous observation that cooking odours have seemed slightly unusual during her seizure period.) There were no "toxic" sequels similar to those seen with hydrogen sulphide.

BAL Vial No. 3—*Success*—This time she sniffed the BAL very early in aura. The lysis of the depersonalization, she reported, seemed to be more rapid. No sequels.

BAL Vials Nos. 4-10 *inclusive*—*Success*—Seizure onset in usual form each time. BAL inhaled early in aura with lysis of depersonalization within three minutes. No sequels noted in any of these trials.

To be certain that the action of the olfactory stimulus in altering the seizure pattern was unrelated to any specific molecular configuration, such as a sulphydryl group, n-ethyl butyrate was again utilized, although it had failed to abort the seizure when it was first inhaled late in the aura. In this second trial of this chemical, it was inhaled before the onset of the "half-way point" and like hydrogen sulphide and BAL it was uniformly successful in aborting the seizures. An alcoholic solution of skatole was tried and this too was effective, as were several haptenes-chemicals of molecular dissimilarity. It was thus apparent that any powerful, unpleasant odour would abort a seizure.

The effect of pleasant essential perfume oils was then studied:

(1) "Essence of Lavender" and "Bergamot Messina," which were described by the patient and 5 control subjects as "fragrant and pleasant" and of "moderate to mild" intensity were totally unsuccessful in aborting the fits.

(2) A larval form of epilepsia cursiva was produced by "Rose Bouquet," described by the patient and 5 controls as "fragrant and pleasant" and of "moderate to mild" intensity. A desire to run was briefly felt by the patient just before the endogenous odour appeared. This peculiarity was the only indication that "Rose Bouquet" had slightly affected the physiological mechanism of the seizure.

(3) A "mixed bouquet," described by the patient and by 5 controls as "sweet and slightly unpleasant" (the patient found it slightly nauseating) and of "moderate to powerful" intensity, produced a partial success. The odour was inhaled early in the stage of depersonalization. Slow lysis of depersonalization resulted but the patient complained of a "cottony" and "fuzzy" feeling in the head. (She spontaneously remarked that these sensations were identical to those experienced after the use of hydrogen sulphide, sequels which were at first considered to have been "toxic.") This "cottony" feeling persisted for three to four hours, during which time she experienced no depersonalization. The patient was convinced

that the seizure had been aborted, when she suddenly experienced her usual olfactory hallucination followed immediately by the voice and *grand mal* convulsion. She had not previously experienced the olfactory hallucination without the prolonged development of depersonalization and anticipatory smell—which had apparently been suppressed by this intermediately unpleasant and strong perfume. (This same phenomenon in a milder form may have been experienced in BAL Vial No. 2.)

(4) The only case of complete success in aborting a seizure by means of an essential perfume oil was that in which pure jasmine was utilized. The patient and 5 control subjects all described this odour as "sweet and definitely unpleasant" with "strong" intensity. This material worked as successfuly as dimercaprol, hydrogen sulphide, n-ethyl butyrate, skatole and the haptenes.

The results of these trials with essential perfume oils when listed in this sequence, strongly confirm the observation that strong, unpleasant odours abort this patient's seizures.

The bizarre fragmentation of the patient's seizure pattern by the use of one pleasant perfume and one slightly unpleasant perfume of different intensities suggests a technique for studying the specific physiological mechanisms of seizure inhibition. Since "pleasant odours" in high concentrations are unpleasant, the seizure inhibiting mechanisms, and their partial variants, can perhaps be titrated by dilution methods. This study has been started.

ELECTROENCEPHALOGRAPHIC STUDIES

In order to gain further insight into the precise physiological effects of these various olfactory stimuli in aborting the seizures, electrical recordings were taken during a seizure induced with metrazol.

Method.—The metrazol activation was performed by the technique of Merlis *et al.* (1950) in which 25 mg. was administered every thirty seconds until the first seizure manifestations were observed either electrically or clinically.

The recording was taken on a Grass Model III-D eight channel electroencephalograph. Electrodes were placed over the convexity of the head and two tympanic as well as two sphenoidal leads were used. The tympanic leads were constructed by the method of MacLean and Arellano (1950) and were applied to a cocainized tympanic membrane. The sphenoidal electrodes consisted of polyethylene coated steel lumbar puncture needles inserted into the naso-pharyngeal mucosa on the right and left sides of the sphenoidal sinus. The exposed tips of these electrodes lay not more than 1.5 to 2.0 cm. from each uncinate gyrus. Local application of cocaine facilitated the placing of these electrodes but great care was taken to avoid anesthetization of the olfactory mucosa.

Results.—After 50 mg. Metrazol had been administered the patient reported that she felt as if she were "floating away" but that the sensation she then experienced was completely unlike her usual depersonalization. After 75 mg. had been given this feeling of strangeness became associated

with fear and anxiety, still unlike her usual aura but similar to the usual metrazol response. The infusion was stopped at this point and no further metrazol was administered.

Three minutes after the termination of the infusion, the patient suddenly reported that she had just experienced her *usual* state of depersonalization and that she would develop a seizure. She said that the seizure was "more advanced" in its course than was the case with her spontaneous fits. At this time the EEG did not reveal any changes from the control period (fig. 1). About ninety seconds after she had given indication that a fit had commenced, she reported that she was nearing her subjective "half-way point." Two minutes and ten seconds after her first indication of a seizure a brief burst of spikes was recorded from the left uncinate area (fig. 2). Twenty-two seconds after this first burst the patient stated that she was just about to reach the stage of anticipatory smell. Twenty-eight seconds after the first burst vigorous spiking was recorded from the left uncinate area with associated, but delayed spikes, in the right uncinate area (fig. 3). In all three figures the tympanic leads provided excessive sixty-cycle artefact which rendered them useless for interpretation. Nevertheless, the spikes in the sphenoidal area were well demonstrated. Immediately upon recording this burst of spikes, pledglets of cotton soaked in BAL were applied under her nares. One further burst of spikes was recorded a few seconds later from the left uncinate area following which the electrical record remained normal. Forty-five seconds after inhaling BAL the patient reported that she was certain that the seizure had been aborted. The record remained unchanged for the next half-hour.

Because of the potential danger to the patient, should she have a convulsion with tympanic membrane and sphenoidal electrodes of rigid steel in these positions, the procedure was not repeated to observe the further effect on the EEG if the BAL or another odour was not administered. A spontaneous convulsion had been previously recorded with surface electrodes which showed, in the clonic phase, a typical pattern in all leads.

DISCUSSION

Successful therapy in this case, though originally based on the generally accepted theory of pathway usurpation, is nevertheless inconsistent with this formulation.

There are three findings which make this hypothesis untenable: (1) The earlier in the course of the preliminary stage of mild depersonalization the exogenous odour was administered, the faster was the lysis of this condition. It was unnecessary to wait for the moment just before the particular sensory aura occurred to introduce the stimulus. (2) The lysis of the depersonalization instantly followed inhalation. Had the conception of a "refractory gap" been correct, we would have expected a continuous progression and maturation of the depersonalization until the half-way

point was reached. But the fact that the exogenous odour was effective *at once*, provided it was applied before the stage of anticipatory smell, shows that it is not a question of "blocking" transmission, but rather of inhibiting a discharge at an early phase of its development. (3) The recording of spikes from the uncinate area and their disappearance within eight seconds after BAL inhalation suggests that although the area had already been partially activated or stimulated, the exogenous odour was still effective in arresting the seizure. Jasper's (1949) records also show that in Jacksonian motor fits the frequency of the spiking activity increases to a high level in a given area of the cortex before that particular part of the extremity begins to twitch. The convulsive movement does not result until a large number of neurons are discharging synchronously.

Gowers' theory assigns a rather passive role to the incoming sensory stimulus, that of merely discharging a specific region of normal cortex at just the right moment to block the march. This should produce an all-or-nothing response; the stimulus either renders the area refractory or it doesn't.

Yet Gowers himself mentioned side effects, stating, "This sudden alteration, in some cases, by opposing suddenly a considerable resistance to the discharge, appears to divert it into other paths, and I have met with cases [which he does not describe] in which the arrest of attacks by the ligature, and still more by the blister, was attended by so much giddiness and other distressing feelings, that the patients declared that the arrested fit was worse than the full attack. Such cases are, however, not frequent."

Similar side effects were noted by our patient and described as a "cottony," "fuzzy" feeling in the head and lightheadedness. Side effects, not mentioned by Gowers, which were also experienced by this patient were (1) running fits of various degrees of severity, (2) circling attacks, and (3) temporary but complete arrest of the seizure with a later recurrence in a more advanced stage of the psychic sequence. Any theory which may be created to explain the success of this form of therapy must also give explanation for the failures and for the side reactions. Gowers' own formulations do not do this.

It is necessary, therefore, to visualize a different mechanism for the effectiveness of afferent stimuli—one essentially based on a principle of active inhibition of the pathological process.

At this point we must re-examine our initial assumption that the sequence of events represented a "march" of excitation within the cortical network. If this assumption is unwarranted, the theory of pathway usurpation is not so much wrong, as it is inapplicable. There are several findings, in no way conclusive, which tend to discredit it: (1) The prolonged duration of the seizures in this patient is inconsistent with the speed of transneuronal spread in the cortical network. Using McCulloch's (1949) figures of 10–30 mm. per second for the transmission speed of such

a wave, depending on depth of anesthesia, it is clear that this woman's brain would have been circled several times by the "march." It is possible, of course, that McCulloch's figures are inapplicable to the unanæsthetized patient. (2) During the prolonged "march" no EEG disturbances were ever recorded. This too, may be misleading because scalp electrodes were used for the most part and direct electrocorticograms could not be taken.

Several other possibilities can be suggested to explain the sequence of this patient's hallucinations: (1) The electrical disturbances may be *static* and may "fire" into a remote area when the proper thresholds have been reached. (2) The appearance of new symptoms may result, on the other hand, not from a spread, either contiguous or to a remote area, but from an alteration in the characteristics of the electrical disturbances in one area alone. (3) The symptoms may be due to a complex combination of excitation of one "centre" with inhibition of another. Present knowledge does not permit us to choose between these alternatives. In this ignorance of the pathogenesis of the patient's symptoms it is much more difficult to find a physiological explanation of the success of the therapy.

There are, however, several findings about which a tentative hypothesis may be constructed. In the first place, the sensory stimuli discovered to be effective since ancient times have been subjectively unpleasant or painful. This has been amply confirmed in the present study in which substitution of various perfume oils points out the possibility of titration of clinical results with varying degrees of unpleasantness. Secondly, the nociceptive stimulus must be "appropriate" to the type of fit. Although some non-specific noxæ have been successful it seems likely that the sensory pathways stimulated must bear some relation to the subjective symptoms of the patient—the ligature about the finger first involved in a Jacksonian fit and the exogenous odour in uncinate fits. Thirdly, the timing of the incoming stimulus is important. There is a time beyond which the stimulus is no longer effective. Considerable variability, however, is permissible early in the seizure and the evidence shows that the earlier the antagonistic stimulus is applied, the more successful will be the result. Fourthly, the fragmentation of the seizure pattern and the production of side reactions by stimuli inappropriate in intensity, quality or timing, or all three in mixed, and as yet unknown, proportions, shows that we are dealing with a mechanism which is by no means organized on an "all-or-none" basis. Lastly, there is one observation, made by this patient, which may be of importance. She noted that the sense of depersonalization suddenly disappeared when the *unpleasant* olfactory hallucination appeared. The lysis of the depersonalization in the course of an uninterrupted fit is quite similar to that produced by the exogenous odour used in the therapy. We may speculate that the endogenous odour activates the same inhibitory mechanism as is activated by an exogenous odour, used earlier in the seizure. It is necessary to postulate that the

endogenous odour, while inhibiting the mechanism producing depersonalization, has concurrently precipitated the next phase of the seizure.

It would, for these reasons, seem plausible to explain the effects of the odour in patients with uncinate fits, as well as the ligature in Jacksonian fits, by postulating the activation of a *localized* inhibitory system. Gellhorn (1947–1948) has shown the activation of a widespread "suppressor" system by violent nociceptive impulses. It is likely that milder nociceptive stimuli activate more restricted, localized "suppressor" or "inhibitory" systems in that particular area of the sensory cortex where they are primarily received—explaining the fragmentary inhibition for the least nociceptive impulses. The stronger the nociceptive influence, the more generalized the activation of the "suppressor" areas becomes. Whether this inhibition is based on a phenomenon similar to Leao's "spreading depression" or to Dusser de Barenne's "suppressor strips" (as seems more likely) remains to be determined.

Counter-stimulant therapy is likely to be effective only in those cases in which there is a well demarcated focal aura. When such an aura occurs, it is possible to activate the local inhibitory system by a stimulus of the appropriate modality—and of an intensity which can be tolerated. If the "wrong" modality is chosen, the intensity of the stimulus might have to be so great, to activate a more widespread inhibitory system, that it could not be tolerated by the patient.

Summary and Conclusions

(1) Uncinate seizures in one patient were consistently aborted by the use of powerful, unpleasant olfactory stimuli.

(2) There was no relation between the molecular configuration of the chemicals which were effective in arresting the fits.

(3) The effectiveness of the therapy was not dependent on psychological suggestion.

(4) The generally accepted theory explaining sensory inhibition of fits was found inadequate. An alternate theory was proposed.

I wish to thank Capt. F. H. Ocko, Medical Corps, U.S. Navy, Chief, Department of Neuropsychiatry, St. Albans Naval Hospital, for his advice, criticism, and repeated psychiatric examination of the patient; and Cdr. P. J. Giotta, Medical Corps, U.S. Navy, for technical assistance in securing sphenoidal recordings.

LEGENDS FOR PLATES

PLATES XIV AND XV

FIGS. 1, 2 and 3.

In all three figures the recordings are arranged, from top to bottom, in the following sequence: (*a*) Left frontal to left tympanic membrane; (*b*) Right frontal to right tympanic membrane; (*c*) Right to left tympanic membranes; (*d*) Left midtemporal to left tympanic membrane; (*e*) Right midtemporal to right tympanic membrane; (*f*) Right anterior temporal to right frontal; (*g*) Left frontal to left nasopharyngeal; (*h*) Right frontal to right nasopharyngeal.

PLATE XIV

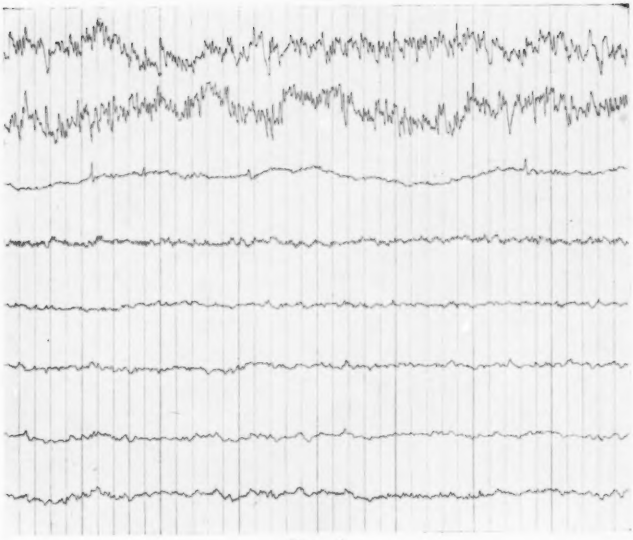

FIG. 1.

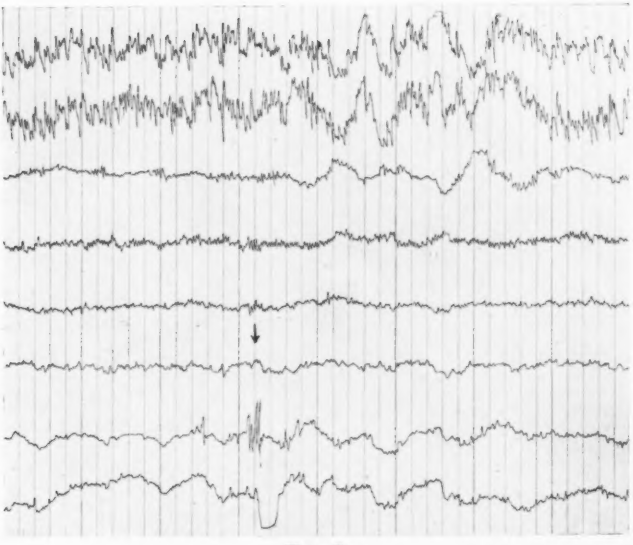

FIG. 2.

To illustrate article by Robert Efron.

PLATE XV

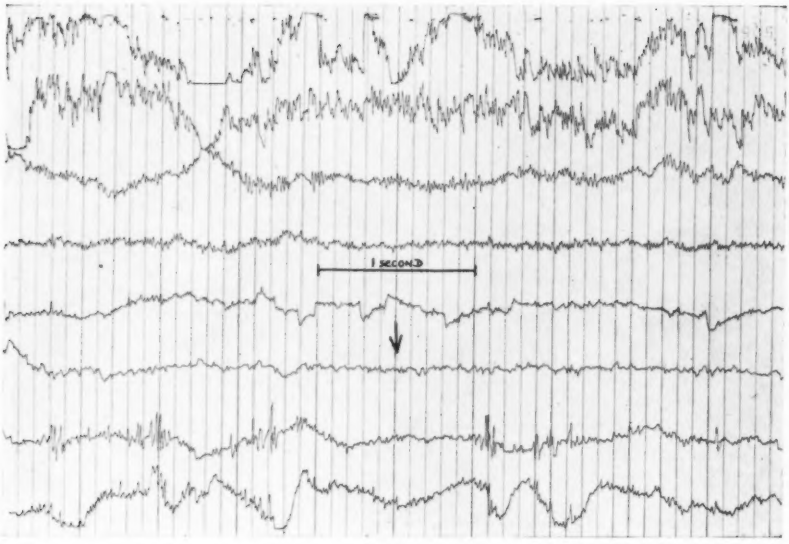

FIG. 3.

To illustrate article by Robert Efron.

The voltage calibration for the first two channels (*a* and *b*) is 10 mm. for a 10 microvolt impulse. For the remaining six channels a deflection of 1 mm. represents 10 microvolts. The time scale is the same for all three figures, the paper moving at 60 mm. per second.

60 cycle artefact was recorded in channels connected to either tympanic membrane lead. Very little of this artefact was recorded from the nasopharyngeal leads and the spikes seen in fig. 2 and fig. 3 can easily be seen superimposed.

The arrow in fig. 2 indicates the first burst of spikes from the left uncinate area. The arrow in fig. 3 indicates the moment BAL pledglets were applied to the nares.

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SOME OBSERVATIONS ON ATYPICAL FEATURES IN ACOUSTIC NEUROMA

BY

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SINCE Cushing's monograph (1917) on "Tumours of the Nervus Acusticus and the Syndrome of the Cerebellopontile Angle," the clinical diagnosis of this tumour in most cases has become a relatively straightforward matter. However, there remains a small but significant group, in which the diagnosis may be extraordinarily difficult.

There have been several publications since Cushing's Paper, some of them concerning many cases. There has been little attempt in these papers to present the difficulties that may arise before a correct diagnosis is made. It is pertinent to recall Cushing's words on this aspect of the problem. After remarking that the correct diagnosis is often made by the House Officer from the history, this author writes: "But it is not always so simple, for with every case there is something new and the moment one begins to feel an overweening confidence in his diagnostic saddle, he is pretty sure to take a cropper."

We were given some insight into how complex the problem can be during our observations on 4 patients in this group (Cases 6, 7, 8, and 12). These form the basis of our report, and were studied at the Maida Vale Hospital. They were admitted between 1951 and 1953 inclusive, and were selected from a group of 14 patients in whom a diagnosis of unilateral acoustic neuroma was made during that period. The other cases reported here were collected from the records of the London Hospital of the last seventeen years (1937-1953 inclusive). 66 patients with unilateral acoustic neuroma were admitted during this period. Our paper is concerned with 18 patients drawn from the total of 80 seen at the two hospitals during the periods already stated. The group is not a large one, understandably so, as it concerns one part, only, of this interesting subject. Small though this series of cases is, it forms 22½ per cent of the total number of patients in whom a diagnosis of unilateral acoustic neuroma was confirmed.

Histologically a benign tumour, an acoustic neuroma, is a dangerous lesion because of its situation in a neighbourhood crowded with vital

structures. If removed while small, the patient is usually cured except for a facial paresis. If removed when large, the immediate mortality is greater, and the possibility of permanent disability, particularly distressing ataxia, is much increased. The danger of blindness from unrelieved hydrocephalus is very real, and the preservation of useful vision must always be an added incentive to early diagnosis. As will be seen from the case reports, the presentation, especially in the older age group, can be so atypical as to be mistaken for cerebral arteriosclerosis, or for some other condition. In this way, valuable time is lost, and the successful removal of the tumour may become impossible. It was with the above considerations in view that we were prompted to present this paper.

The most complete early report on the clinical and pathological aspects of a case of acoustic neuroma was made by Jean Cruveilhier in "Anatomie Pathologique du Corps Humain," Volume II (1835–1842). Cushing gives a complete translation of this report in his monograph. The first accurate clinical localization of an acoustic tumour was made by Stevens (1879). Oppenheim (1889) is usually credited with the first correct localization based on clinical symptoms of a tumour of the angle—although Cushing gives priority to Stevens.

In 1900 Sternberg collected many examples of "Acoustic Tumours," added 4 cases of his own, and gave a clear pathological description of the lesion. In this year, also, Monakow reported a case of neurofibroma or fibrosarcoma of the eighth nerve which had been correctly diagnosed and localized during life. He suggested on the basis of the post-mortem appearances that such lesions might be favourable for operative removal. In 1902, Hartman reported on 26 cases from the German literature, and suggested the general term "Recess Tumours." In the same year the term "Cerebellopontile Angle Tumour" was suggested by Henneberg and Koch.

In 1915, Henschen reported on a series of patients with tumours of the cerebellopontine angle, with particular reference to the acoustic neuroma. Cushing (1917) described in detail the clinical features, findings at operation, and the histological appearances in 30 cases of acoustic neuromas. On the basis of this study, he stated "The symptomatic progress of the average acoustic tumour occurs more or less in the following stages:

first, auditory and labyrinthine manifestations;
second, the occipito-frontal pains, with suboccipital discomforts;
third, the inco-ordination and instability of cerebellar origin;
fourth, the evidence of involvement of adjacent cranial nerves;
fifth, the indication of an increased intracranial tension (with a choked disc, and its consequences);
sixth, dysarthria and dysphagia, and *final*, cerebellar crises and respiratory difficulties."

The above chronological sequence of symptoms has been referred to

with greater emphasis by later authors—Parker (1928), List (1933), Olsen and Horrax (1944). The last two authors felt this syndrome of symptomatic progression according to a definite chronology, to be almost infallible, and that some other tumour was likely if the complex was not typical. They analysed a group of 42 patients operated upon at the Lahey Clinic, between 1932 and 1942, with special reference to atypical features. They pointed out the *absence of deafness* in 2 patients.

Edwards and Patterson (1951), in their analysis of 157 cases, state: "Although acoustic symptoms were among the first to appear in 75 per cent of patients, a fair number complained of other symptoms. For this reason, we believe that the chronological order of symptoms defined by Cushing (1917), has little practical value in helping to establish an early diagnosis, and we feel that some others have accorded it too much importance." Lundborg (1952), in his paper on 300 cases, states: "The course in almost every third case deviates from the norm." To avoid repetition, further references to the literature will be mentioned in the discussion which follows.

If the criteria for diagnosis of a certain lesion are made too rigid, then that lesion will not be diagnosed in the absence of these criteria. We feel that there is a tendency for this to happen in the diagnosis of the eighth nerve tumour, more especially as the criteria are indeed present in the majority of instances. Most papers on acoustic neuroma since that of Cushing have dealt with large series of cases. We feel this has resulted in a tendency for the unusual or atypical cases to be overshadowed by the larger number that are typical. Our attention has been mainly confined to a small number of cases, each of which departs in one or more ways from the previously accepted pattern.

In regard to atypical features, it should be noted that in Cushing's 30 cases, 6 (Cases 7, 11, 18, 20, 22, 29), presented with symptoms and signs unlike his description for the group as a whole. Cushing made this clear on his commentary on each of the cases. Lundborg (1952), in his analysis of 300 cases from Olivecrona's Clinic, states that 68·3 per cent presented with typical chronology, 12·7 per cent had atypical presentations, and in 12·3 per cent all the symptoms occurred concurrently. Parker (1928) made the following statement: "Tumours arising from the eighth cranial nerve produce a clinical syndrome so well known as not to need further description." He then stated: "There are certain variations from the average law referable to cranial nerves other than the eighth, e.g. facial spasm and neuralgia of the trigeminal."

Revilla (1947) stated that only 31 per cent had a symptomatic progression in accordance with the usual chronology, as laid down by Cushing. In no less than 12·4 per cent headaches and suboccipital discomforts preceded auditory symptoms. In 6 per cent there was no definite pattern. He pointed out that the mode of onset of signs and symptoms from the in-

volvement of the cerebellopontine angle structures, was not of such a rigid pattern as laid down by Cushing, and reiterated by later writers. He discussed variations in time relations of involvement of various structures in the angle.

In our own material, although we have several examples of this type of variation, they are not included in this paper. We have restricted ourselves to cases, in most of which the whole natural history was bizarre and very different from accepted standards. These cases comprised *over one-fifth* of the total number of patients with unilateral acoustic neuromas available for study.

The acoustic neuroma, according to classical concepts, first involves structures in the lateral part of the cerebellopontine angle. However, we believe that in a proportion of patients with eighth nerve tumours (probably 20–25 per cent), the growth begins medially, and so involves the brain-stem early in its natural history. Because of this, symptoms due to direct pressure on the brain-stem, or indirectly due to hydrocephalus, occur early. Conversely, symptoms and signs, due to involvement of lateral structures in the angle, may be long delayed or remain absent. Even deafness may not occur.

We believe that in our cases, the variations from the typical pattern in the histories can be explained on the assumption that hydrocephalus may occur early in some patients, and that direct brain-stem pressure may be present without any other manifestations of the syndrome. In some cases the symptoms and signs are more easily explained as being due to combined hydrocephalus and pressure on the brain-stem. These effects of the tumour may exist independently of clinical involvement of the cranial nerves in the cerebellopontine angle. This may be due to either the medial situation of a small tumour, or continued conduction in greatly stretched and distorted nerves. This last point is further developed in the section on deafness.

CASE REPORTS

The 18 case reports forming the basis of this paper, will be arranged to illustrate each part of the discussion. These reports, although long, are necessary to illustrate our main theme, namely, that of the importance of recognizing unusual natural histories of the disease. 4 of the cases (6, 7, 8, and 12) were personally studied by us, and will be set down in rather more detail.

Lumbar Puncture: pressure readings were recorded in millimetres of cerebrospinal fluid, and protein estimations in milligrams per 100 c.c. (in the reports that follow, only the number will be stated, the unit of measurement being understood).

The following criteria have been employed for arriving at a positive diagnosis of acoustic neuroma.

(1) A tumour was removed at operation, or found at post-mortem, which had the histological characteristics of a neurofibroma (schwannoma, neurinoma), and either (*a*) had eroded the porus acousticus as seen at operation, or at post-mortem, or (*b*) was definitely seen to arise from the auditory nerve.

(2) The other nerves in the cerebellopontine angle were seen to be free from tumour—although they might be stretched and distorted by that tumour.

The problems will be considered under six main headings:

(A) Deafness. (B) Other Eighth Nerve Symptoms. (C) Hydrocephalus (acute and chronic). (D) Combined Hydrocephalus and Brain-stem pressure. (E) Brain-stem pressure. (F) Involvement of Other Structures in the Angle.

(A) *Deafness*

Unilateral deafness is important in the evaluation of the symptom complex of a patient who may have an intracranial tumour. If progressive, it is of even greater significance. Unilateral deafness in middle or old age should not be lightly dismissed if it occurs in a patient who, on other grounds, is suspected of having a space occupying lesion. However, it is not unusual to find that little regard is given to this symptom by the patient or his medical advisers. All too often it is explained away as being "due to old age," or attributed to arteriosclerosis or some other equally indefinite cause.

13 of our patients complained of deafness, this being elicited by direct enquiry in 8, and volunteered in only 5. Most of the 8 patients thought their deafness was unimportant and ascribed it to some other event—bomb explosion, blast, previous illness, etc. *The importance of direct enquiry for deafness in all tumour suspect cases is plainly evident.* In a further patient, deafness was present on examination.

This symptom was inaugural in 9 patients only. In patient 2, it was the last among many other symptoms. This sign was given its true value, and a correct diagnosis made, in 4 only of the 14 patients found to be deaf. In 3 of these, there was supporting evidence in suspicious erosion of the internal acoustic meatus. In Cases 9 and 12, deafness was regarded as being significant only after several weeks in hospital.

The importance of deafness in localizing a tumour in the posterior fossa and, further, in the cerebellopontine angle, is clear from the fact that 5 of our patients who presented with mental symptoms were also deaf, and there was *nothing else to localize the lesion.* We thus see that deafness attains even greater significance in patients with atypical symptoms than in those in whom the classical syndrome is well developed.

4 of our 18 patients were *not* deaf on clinical testing. This is a striking fact, and requires further comment. The cochlear and vestibular divisions of the auditory nerve may be regarded as consisting of two portions on

the basis of histological differences in the supporting tissues, a proximal and a distal, each of about 1 cm. in length. The proximal portion extends from the attachment of the nerve at the ponto-medullary junction to the internal auditory meatus, and the distal portion lies within the meatus. Henschen, in his earlier work (1910), was of the opinion that most tumours arose from the distal portion of the vestibular division. In his later paper (1915), he suggested that some tumours may arise from the proximal portion of the nerve. This suggestion was made on the basis of 2 patients, 1 of whom still preserved some hearing, and in both of whom the hearing loss was late in appearing. Cushing, in his report of his Case 22, refers to Henschen's paper and states: "The fact that all the few early tumours which have been encountered have had a distal seat of origin, more or less within the porus, speaks strongly in favour of this part of the nerve as the more usual starting point of the lesion, but the number is few, and there seems no definite reason why the growth should not take its start elsewhere. It is probable that an acoustic tumour originating in the proximal and free portion of the nerve, would be capable of a much greater enlargement without impairment of function than if the fibres suffered from compression within the bony canal. It is well known that tumours of the peripheral nerves may reach a remarkable size without appreciably interfering with transmission of nervous impulses, and even when impaired normal function may be resumed after enucleation of the growth." After stating that in 25 of his 30 cases the acoustic symptoms were inaugural, Cushing wrote: "In some cases there is no definite priority. The literature contains many cases with similar case histories, and we must accept the fact that the acoustic symptoms may long remain latent."

It should be admitted that audiometry was performed on only 1 of our 4 patients who were found not to be deaf on routine neurological examination. Of the tests for deafness, Cushing had this to say: "Absolute deafness is almost as difficult to certify as an absolute loss of the vestibular reactions."

(B) *Other Eighth Nerve Symptoms*

9 of our patients had vertigo, and 7 tinnitus. All the patients with vertigo were also deaf. Occasionally, tinnitus, when unassociated with deafness, may be of localizing value. It was present, for example, in Case 3, although this patient was not deaf. Acoustic symptoms occurred as an initial complaint in a high proportion of patients in most of the published series. They were present in 50 per cent of Henschen's cases (1910), in 25 out of Cushing's 30 cases (1917), in 73 per cent of List's cases (1933), in 68·6 per cent of Revilla's cases (1947), and 71 per cent of Lundborg's series (1952). We see, therefore, *that there remains over a quarter of all patients with some other presenting symptoms.*

Clearly, if a patient is suspected of harbouring an acoustic neuroma, then both caloric and audiometric examinations should be carried out—

and the apparent absence of deafness on ordinary clinical grounds should not deter one from carrying out these valuable investigations.

In concluding this section, we would, therefore, emphasize that:

(1) Progressive unilateral deafness should never be lightly dismissed.

(2) Unilateral deafness associated with mental or motor symptoms (later discussed in detail) in a middle-aged or elderly person, may very well be due to an acoustic neuroma.

(3) In all patients with symptoms and signs which may be due to brain tumour, careful enquiry should be made in regard to deafness.

(4) Clinical deafness is not essential for a diagnosis of acoustic neuroma; but in the presence of normal hearing, and of normal function in other nerves in the cerebellopontine angle, radiological aid is essential. A patient suspected of having an acoustic neuroma should not be accepted as having normal hearing unless an audiogram has been done and found to be normal.

(C) *Hydrocephalus*

In his book on "Diseases of the Nervous System" (1951), Brain defines hydrocephalus as "an increase in the volume of cerebrospinal fluid within the skull." He then draws a distinction between two main types of hydrocephalus: "(1), increase in the volume of cerebrospinal fluid without increase in its pressure, and (2), increase in the volume with increase in the pressure." In this definition, the size of the ventricles is not mentioned, their dilatation, though usual, is not necessary for the presence of hydrocephalus, the cerebrospinal fluid increase being accommodated in the subarachnoid space.

The term hydrocephalus may also be used to explain a clinical concept, in which there is a definite elevation of the intracranial pressure, giving rise to one or all of the triad—headache, vomiting, and papillœdema. In most of those patients presenting in this way, with the lesion in or near the mid-line, or in the posterior fossa, the ventricles will be dilated. This is not invariable, however, the ventricles occasionally being normal in size, or even small. In space occupying lesions above the tentorium, and not situated near the mid-line, the ventricles may be compressed, and the fluid displaced from the subarachnoid spaces, so that hydrocephalus, according to the anatomical definition, does not exist. Even so, the clinical concept is often applied to such cases.

As ventriculography was not carried out in all of our patients, both the clinical and anatomical concepts of hydrocephalus have been employed in our discussion. In all the acute cases, there was very definite evidence of raised intracranial pressure, and in those patients subjected to ventriculography, the ventricles were dilated, in some cases grossly so. In the patients assigned to the group, chronic hydrocephalus, the clinical evidence of raised intracranial pressure was, on the whole, less apparent, but in all except one of this group, the ventricles were seen to be very

obviously dilated. In the one patient (Case 11) in which there was no visual evidence of ventricular dilatation, there were very marked changes due to raised pressure, these being bilateral papillœdema, skull X-ray changes, and a lumbar puncture pressure of 410.

Hydrocephalus is common in patients with acoustic neuromas, and usually regarded as appearing late in the history. If papillœdema is used as an index of its frequency, it was present in 97·5 per cent of Henschen's cases (1910), in all of Cushing's 30 cases, and in 76 per cent of Edwards' and Patterson's 157 cases (1951). Papillœdema was present in 14 of our cases, but in 17, there was evidence of hydrocephalus. In one patient (Case 14) there was no evidence to suggest raised intracranial pressure.

As mentioned earlier, we believe that hydrocephalus occurs *early* in a proportion of patients with acoustic neuromas. There is little room in the cerebellopontine angle or recess for other than the structures which normally cross it. An acoustic neuroma, or any other recess tumour, is accommodated partly by occupying the small space available, but mainly by compression and distortion of the structures forming the boundaries of this space—pons and medulla, cerebellum, fifth, seventh, and eighth cranial nerves, and internal acoustic meatus. However, it is probable that there is a variation in size of this angle, and possibly also of the brain-stem. This variation would be one explanation of the differences in behaviour of acoustic tumours with respect to compression of the brain-stem, and the production of an obstructive hydrocephalus and motor signs in the limbs. Another explanation is to be sought in the site of the main mass of the tumour in relation to the brain-stem. If it is closely applied to the stem, suggestive of a medial site of origin of the tumour, then the symptoms and signs of hydrocephalus and brain-stem compression might be expected to appear earlier than those due to involvement of adjacent cranial nerves and the cerebellum. Even a small acoustic neuroma may produce hydrocephalus. In 2 of our patients with chronic hydrocephalus, the tumours were quite small. Thus the necropsy report describes them as being "the size of a small green olive" in Case 6, and "the size of a hazel nut" in Case 8. At operation the tumour in Case 7 was described as being "the size of a small walnut." The tumour was large in Case 9 but there had been a previous decompression, and its close relationship to the brain-stem is described in the operation note.

Hydrocephalus can manifest itself in many odd ways, and although it appears to have four main patterns in our own cases (intermittent hydrocephalus, cases with visual failure, early dementia, and motor symptoms), other ways of presentation of hydrocephalus are quite possible.

In the following paragraphs on hydrocephalus, only 12 of the 17 cases with hydrocephalus are selected for discussion. We feel the presenting or important symptoms were due to the hydrocephalus in these 12 cases. In the remaining 6 cases, the association is not so clear and some other

mechanism—such as brain-stem pressure—was felt by us to be more important in the production of symptoms, or at least equal in importance to hydrocephalus.

(1) Acute Hydrocephalus

There were 5 patients (Cases 1, 2, 3, 4 and 5) whose main symptoms were those of acute hydrocephalus—generalized headache, vomiting, and blurring of vision. In particular, fluctuating visual acuity with transient and episodic visual failure, especially in relation to head movement, was a marked feature in these cases. Hearing was normal in 2 patients; in a third, deafness had been present for seven years, but was disregarded by the patient. In all, the acute hydrocephalic symptoms completely overshadowed the others. These 5 patients can be further divided into two groups, as follows:

(*a*) *Intermittent hydrocephalus.*—2 patients fell into this group (Cases 1 and 2). Momentary attacks of mistiness of vision occurred in Case 1 and brief periods of blindness, each lasting for one or two minutes in Case 2. Transient, recurring, episodes of blindness is usually indicative of a lesion at or near the mid-line, which gives rise to intermittent hydrocephalus in its early stages.

The precise mechanism of intermittent hydrocephalus in these cases is not clear to us. It is generally thought to be due to an intermittent block in the cerebrospinal fluid pathways. It seems unlikely that the tumour itself can vary in size or position over short periods of time, and a more likely explanation is an intermittent disturbance of blood supply to the brain-stem, with varying œdema. An alternative mechanism is a variation in the size of an associated arachnoid cyst.

Case 1.—*L. L.* (*L.H.* 11302/54), *female, aged* 32, 24.3.53.

H.P.I.—6 months: momentary sharp pain on extension of neck, radiating forwards from occiput. 3 months: attacks of mistiness of vision lasting a few seconds and following sudden head movements. 2 months: increasing difficulty in seeing in the dark. Deafness in the right ear—on direct enquiry, for one year, which she ascribed to paratyphoid fever.

Examination.—Bilateral papillœdema. V.A. left and right 6/4. Moderate deafness right ear. E.N.T. examination: conductive deafness over all frequencies, right ear.

Investigations.—Caloric test normal. Ventriculography and A.E.G. combined: Symmetrical hydrocephalus, dilated third ventricle. Poor filling of aqueduct and fourth. Upward displacement of third ventricle.

Diagnosis.—Prior to ventriculography, mid-line tumour possibly colloid cyst of third ventricle. Acoustic neuroma thought to be unlikely. Later developed depression of corneal reflex.

Operation.—Unilateral exposure of right side of posterior fossa, with removal of moderate-sized tumour. This indented the pons considerably, and had a large cyst associated with it.

Comment.—A very short history of hydrocephalic symptoms and signs

with a deaf right ear which was considered insignificant in the history by the patient who was a nursing sister, and the attending physician because of the normal caloric tests till just before the operation, when a reduced corneal reflex, and raised cerebrospinal fluid protein made the diagnosis more likely, though not by classical standards.

Case 2.—*L. W.* (*L.H.* 19210/50), *male, aged* 26, 5.7.43.

H.P.I.—2 years: diplopia lasting for one month. 1 year: attacks of transient blindness lasting 1 to 2 minutes and coming on during violent head movement. Progressively more frequent. Lost consciousness on one occasion. 3 months: night vision difficult. Unsteadiness. 1 month: headaches, vertigo, tinnitus, deafness right ear. Presenting complaint was failing vision. He was first seen in an Army Hospital with gross papillœdema with hæmorrhages and exudates, but at that time no headache.

Examination.—Cranial Nerves: Chronic bilateral papillœdema. Secondary optic atrophy right side. V.A. right J.20, left J.6. Coarse nystagmus. Diminished right corneal reflex. Very slight deafness right ear. A.C. greater than B.C. Limbs: No ataxia. Walks on a wide base.

Investigations.—Skull X-ray: Evidence of raised pressure. Lumbar Puncture: High pressure. Protein 450. Caloric Test: Inactive right labyrinth.

Diagnosis.—Right acoustic neuroma.

Operation.—A large acoustic neuroma removed.

Comment.—The clinical history of episodic loss of vision was somewhat atypical of an acoustic neuroma, but the physical signs and investigations pointed to the correct diagnosis. Deafness, vertigo and tinnitus were last and most insignificant in the story; it was also notable that in view of the gross eye signs and symptoms suggestive of hydrocephalus the headaches should have come so late in the story.

(*b*) *Cases with visual failure.*—In 3 patients comprising this group (Cases 3, 4, and 5), the main symptom was visual disturbance. The physical signs, too, seemed mainly limited to the eyes, and there was little to suggest a posterior fossa localization for the lesions. There was a marked difference between the two eyes in all three cases. Patients 3 and 4 each had a blind eye, the acuity in the other remaining relatively good, 6/36 and 6/12, and both had papillœdema, with secondary optic atrophy. Both had extremely slight bilateral cerebellar signs and no classical signs of cerebellopontine angle involvement—not even deafness. There being some similarity between these features and those of the Foster-Kennedy Syndrome, an anteriorly placed tumour seemed more likely than an acoustic neuroma. Patient No. 5 had a nearly blind left eye, and a visual acuity of 6/36 in the right eye. Direct enquiry revealed that she had been deaf for seven years, but in view of the marked visual signs, this fact was disregarded in the early appraisal. Later, when cerebellar signs developed on the same side as the deaf ear, the correct diagnosis was made, though there were still no other signs of an angle tumour.

Case 3.—*H. F.* (*L.H.* 28456/50), *male, aged* 36. 15.10.47.

H.P.I.—16 months: mild right frontal morning headache. 12 months: a few

episodes of transient obscuration of vision occurring once weekly, with head movements. 6 months: two episodes only during this period, of staggering to the right. 3 months: tinnitus. 7 weeks: progressive blurring of vision in left eye. *No deafness or vertigo.*

Examination.—Mental state: normal. Cranial Nerves: moderate papillœdema, right eye. Optic atrophy, left eye (probably secondary). V.A. right 6/5, left 1/60. Horizontal and vertical nystagmus. Limbs: Bilateral ataxia, right worse than left. Seen by E.N.T. Surgeon, hearing normal.

Investigations.—Lumbar Puncture: Pressure 280, protein 180. Left Carotid Arteriogram: Unusual vascularity near left sphenoidal ridge.

Diagnosis.—Left sphenoidal ridge meningioma.

Operation.—Left frontal exploration—negative.

Further course.—No new signs appeared after two months, and a ventriculogram was done. This showed gross hydrocephalus, with no filling of the aqueduct or the fourth ventricle. Diagnosis of a right cerebellar hæmangioblastoma was considered, and a posterior fossa exploration carried out, a very large right acoustic neuroma being found. This had displaced the fifth nerve considerably, and the seventh nerve was passing through it.

Comment.—The diagnosis in this case rested between a right cerebellar or a left frontal lesion; the difference between the two eyes was so gross as to simulate a Foster-Kennedy Syndrome, the ataxia being put down to the secondary effects of a hydrocephalus. After a negative frontal exploration, and with the aid of a ventriculogram, a right cerebellar hæmangioblastoma seemed the correct diagnosis as, pre-operatively, there was no classical clinical evidence to suspect an acoustic nerve tumour. It is of interest to note that there was no deafness or vertigo, and no disorder of the fifth or seventh nerves in spite of these being involved considerably by the neuroma as seen at operation.

Case 4.—*B.W.* (*L.H.* 16055/49), female, aged 24. 22.5.44.

P.M.H.—Treated for "nerves" since childhood.

H.P.I.—5 months: unsteady gait, lurching to left. 5 months: blurring of vision. Attacks of momentary loss of vision. 2 weeks: one attack headache and vomiting. No deafness, tinnitus, or vertigo.

Examination.—Mental State: Rational and co-operative. Unable to give a clear account of her illness. Cranial Nerves: Left anosmia. Bilateral papillœdema, right more than left. Marked pallor of left disc. V.A. right 6/12, blind left eye. Horizontal nystagmus. *No deafness.* Limbs: Doubtful bilateral intention tremor.

Investigations.—Lumbar Puncture: Pressure 300, protein 160. Ventriculography: Gross hydrocephalus. Aqueduct and fourth ventricle not well filled.

Diagnosis.—Left sphenoidal ridge meningioma prior to ventriculogram. Cerebellar glioma following it.

Operation.—Suboccipital decompression.

Further course.—Readmitted 3 months later. No new symptoms. Marked bilateral optic atrophy now present. Nystagmus more marked. Occasional left sixth and seventh palsies. Bilateral cerebellar signs more marked. Tendon reflexes increased in all limbs. Weak left lower limb. Plantar responses flexor.

Investigations.—L.P.: Same findings. Skull X-ray: Normal. Calorics: Normal response.

Diagnosis.—In the presence of active labyrinths, an acoustic neuroma was ruled

out. A cerebellar hæmangioblastoma with an extension into the angle seemed the most likely.

Operation.—A large acoustic neuroma was found almost filling the left side of the posterior fossa. The seventh and eighth nerves were passing into the tumour.

Comment.—Neither the symptoms nor signs suggested an acoustic neuroma; the main signs and symptoms were indicative of a lesion near the left optic and olfactory nerves, the nystagmus was believed to be due to secondary pressure. However, the ventriculogram, the fresh cerebellar, left sixth and seventh nerve signs, with a raised protein, suggested a left cerebellar hœmangioblastoma, probably protruding into the angle. The absent fifth and eighth signs, and the chronology were quite atypical of an acoustic neuroma. It is of interest to note that the eighth nerve was passing into a massive tumour.

Case 5.—S. M. (L.H. 11601/47), male, aged 57. 21.10.47.

H.P.I.—9 months: generalized headaches. 8 months: transient attacks of giddiness, each followed by obscuration of vision for a minute or two. Twenty to thirty such attacks. 6 months: progressive dimness of vision in left eye, ending in blindness. Few weeks: dimness of vision in right eye occasionally. 7 years: deaf, right ear (on direct enquiry).

Examination.—Cranial Nerves: Bilateral papillœdema, right more than left, with secondary optic atrophy on left. V.A. right 6/36, left hand movements. Impaired upward conjugate eye movement. Bilateral deafness, right more than left. Bone conduction present in both ears.

Investigations.—Lumbar Puncture: Pressure 280. Protein 200. Bilateral Arteriography: Evidence of increased pressure only. Two days later, cerebellar signs in the right arm, and a right extensor plantar response, appeared.

Diagnosis.—Before arteriography sphenoidal ridge meningioma was considered. With the appearance of cerebellar signs, a right acoustic neuroma was diagnosed.

Operation.—Partial removal of large acoustic neuroma.

Comment.—As in the previous 2 cases, the history and early physical signs all pointed to a lesion near the optic nerves or frontal region. The deaf right ear was ignored as insignificant till late, when the right arm ataxia made the diagnosis more likely.

The average length of the history of the 5 patients in the complete group was 2 years and 3 months. If the deafness in Case 5 be excluded, then this period is reduced to 12 months; the average age of the patients in this group was 35 years.

(2) Chronic Hydrocephalus

There were 6 patients in whom we felt the symptoms were due to a chronic hydrocephalus (Cases 6, 7, 8, 9, 10, and 11), and a further 1 in which it probably played the major part (Case 13). In the 6 patients, these symptoms were those of altered mental function and personality. A lessening of affect and insight was prominent among these symptoms. Confusion and disorientation, and loss of recent memory were present in some, and apathy and disinterest was very noticeable in Cases 8 and 9.

An actual deterioration in mental performance on formal testing was inconspicuous in all except Cases 8 and 10. Further details of these symptoms are set out in the Case Reports. In 2 patients (Cases 8 and 9), these symptoms were gross, and formed the presenting feature. Both patients were deaf, direct enquiry was needed to elicit this fact, and in neither was it allowed due weight as a localizing feature. Patient No. 8 was thought to have a corpus callosum glioma, and the diagnosis in Case 9 was thought to be a colloid cyst of the third ventricle. In 2 other Cases, 10 and 11, these symptoms were very marked. They were ascribed to hydrocephalus, due to a left cerebellar neoplasm, in Case 10. There was slight deafness only on examination, and the lumbar cerebrospinal fluid protein of 10 mg. was clearly unusual for an acoustic neuroma. In Case 11, the correct diagnosis was made on admission, but the occurrence of epileptic attacks and marked mental deterioration over a period of 15 months is sufficiently unusual to warrant recording. Patients 6 and 7 had mild mental symptoms on admission. Subsequently, the main effect of the tumour in these cases was on the mental and intellectual functions. We were given an opportunity of observing the progressive mental deterioration which occurs when obstructive hydrocephalus is unrelieved.

The average length of the history in these 6 patients was 5 years, and the average age of the patients was 55 years. These figures contrast rather strikingly with those for acute hydrocephalus. They indicate that patients in the older age groups are more prone to develop these so-called "frontal lobe signs" in association with acoustic neuroma. It is precisely in these age groups that the danger of ascribing them to some other cause is greatest. In Case 13 spastic paraplegia was associated with some behaviour disorder. This case will receive further discussion in the next section.

The symptoms arising from the effect on mental function in our cases have been of especial interest to us. There is no reason to suppose that these are due to other than the related hydrocephalus. It is possible that the underlying mechanism is a stretching of the association tracts between the frontal lobes and the upper brain-stem by the distended third ventricle. This would account for the reversibility of the symptoms in early cases following relief of the hydrocephalus. Certainly there are few changes in the cerebral cortex to account for these symptoms in even the advanced cases, as shown in the detailed histological studies carried out on 2 of our patients.

In 1902, a study of these symptoms associated with posterior fossa tumours was made by Schuster. In 1911, Mingazinni, in discussing cerebellopontine angle tumours, states that the psychic phenomena that had been noted by himself and other authors—a condition of stupor, unrest, and excitability—were to be associated with the increased intracranial pressure. In 1914, Fumarola, in a paper on the cerebellopontine angle

syndrome, mentioned 3 cases with definite psychic features. Cushing (1917) referred to psychic disturbances as being "an expression merely of the general increase in tension, associated with an internal hydrocephalus —so called frontal lobe symptoms, characterized by an impairment of the intellectual faculties." He points out, too, that they may occur as early features of the syndrome but are more likely to be a source of confusion with an advanced lesion.

In 1931, mental symptoms associated with cerebral tumours was the subject of a combined meeting of the sections of neurology and psychiatry at the Royal Society of Medicine. Holmes (1931) discussed these symptoms as they occur in states of raised intracranial pressure in general, and with frontal lobe tumours in particular. Brain described their association with tumours of the cerebellum and of the third ventricle and mid-brain. He felt that the mental symptoms in these cases were secondary, and due to the increased intracranial pressure. His first patient, a girl of 19, died from the effects of internal hydrocephalus and the autopsy revealed a tiny polypoid glioma growing from the posterior commissure of the third ventricle and blocking the aqueduct of Sylvius. He described 4 further cases, including 2 aged 48 and 50, in which the mental disturbances were a marked feature and made localization difficult. 1 of these 2 had a cerebellar glioma and the other a vermis angioma; this second patient improved dramatically during operation, which was performed under local anæsthesia. In summarizing, Brain (1931) stated that profound mental disturbances may be produced by tumours in the posterior fossa, and that these seemed more liable to occur in the middle-aged and elderly than in children. He felt that both vascular disturbances, especially œdema, and tension of the brain tissue, were important factors in the production of these symptoms and pointed out that there was no way of distinguishing whether the mental symptoms were produced by the local pressure of the tumour, or by the remote effects. He mentioned the importance of an accurate history and that ventriculography might be of great assistance in doubtful cases.

It has long been recognized that these symptoms, due to an obstructive hydrocephalus from a mid-line or a posterior fossa blocking lesion, are a source of confusion with those due to a frontal lobe tumour. Mistakes in localization, leading to incorrectly planned operations, were not unusual prior to the introduction of ventriculography.

The association of mental changes with acoustic neuromas is not at all uncommon. As a presenting or main feature, however, they are rare. When they do occur they are usually associated with hydrocephalus. Lundborg (1952) recorded these changes in 23·2 per cent of his large series. In 4 patients (1·3 per cent), they were a presenting feature. They included loss of memory for recent events, as with cerebral tumours generally. There were also cases with apathy, lowered initiative, and changes in

temperament and personality. Lundborg does not mention their association with hydrocephalus, but as 72·7 per cent of the series had papillœdema, such an association seems very likely. Neither does he mention how frequent, or of what severity, were the classical signs of the cerebellopontine angle syndrome in these cases with psychic features.

Case 6.—*M. B.* (*M.V.H.* 25704), *female, aged* 69. 8.10.51.

H.P.I.—5 years: tinnitus. Few months: unsteadiness of gait. Few weeks: frontal and occipital headaches and diplopia. 6-7 years: progressive deafness, left ear (direct enquiry).

The history above is not as presented by the patient. She was extremely vague about her complaints, and especially about dates. This made it difficult to elicit a history from her, and much direct questioning was required.

Examination.—Mental State: Lacking in insight, inability to recall events of her illness left her quite undisturbed. Could not perform simple calculations, although recent memory and orientation were normal. Cranial Nerves: Mild papillœdema. Visual acuity 6/12 in both eyes. Slight horizontal nystagmus. Left corneal reflex a little diminished. Slight left sixth paresis and facial asymmetry on the left side. Moderately deaf in the left ear. Limbs: Slight ataxia of left upper limb. Very slight spastic weakness of lower limbs with extensor plantar responses. Evidence of fifth, sixth and eighth cranial nerve involvement, not convincingly demonstrated by all observers. Seen by E.N.T. Surgeon, who demonstrated profound hearing loss in the left ear.

Investigations.—I.A.M.'s: Left porus acousticus not enlarged. Caloric Test: Only slight loss of left vestibular response. Air Ventriculography: Cerebrospinal fluid under slightly increased pressure, contained 60 mg. Symmetrical hydrocephalus of the lateral ventricles, dilatation of the third, and a mid-line fourth ventricle. Myodil Ventriculography: Aqueduct normal on screening but filling of it, and of fourth ventricle, was inadequate for good radiography.

Diagnosis.—Before Ventriculography: a diagnosis of acoustic neuroma seemed likely in spite of the unusual sequence of symptoms. The myodil flowed freely from the aqueduct and fourth ventricle, and the radiological evidence was interpreted as being more in favour of a hydrocephalus, due to atrophy, than to obstruction.

Further course.—Left facial weakness and ataxia of left upper limb became accentuated following ventriculography. Lumbar puncture to assess pressure, and air ventriculography performed. L.P.: Pressure of 210, protein of 38. A.E.G.: Aqueduct and fourth ventricle well filled. Ventricle normal in position but a little dilated. Free flow of air into ventricles was used as evidence against an obstructive lesion.

After the air encephalogram, her condition deteriorated. She became confused and irrational, and was incontinent. Attacks occurred during which she would subside gently to the ground, as in a fit, although there were no associated pulse or respiratory changes, and no abnormal movements of her limbs. There followed a slow improvement in the patient's mental state, and she was sent to a nursing home for a few weeks.

Second admission, three months later: Her mental state had deteriorated, with disorientation, inability to concentrate, poor memory (now involving recent events), and incontinence. Walking also had deteriorated. Physical signs unchanged.

Investigations.—Lumbar Puncture: Two performed. Pressures of 170 and 270, with normal protein. Ventriculography: Pressure moderately raised, protein

raised (30 and 40). Appearances of ventricles unchanged. Sagittal Sinugram: Revealed patent sinus.

Diagnosis.—A definite diagnosis was not made. She was discharged to a nursing home, where she lived for a further ten months, with progressive mental deterioration, and the development of a spastic paraparesis.

Examination of brain: This revealed in the left cerebellopontine angle, an eighth nerve tumour, the size of a small green olive, 21 × 17 × 12 mm. This was indenting the brain-stem, and was histologically typical of a neurofibroma (*see* fig. 1).

There was no surface atrophy of the brain, but gross dilatation of the lateral ventricles was present (*see* fig. 2). There was little dilatation of the third and fourth ventricles, and none of the aqueduct. Sections were taken from all representative parts of the brain and spinal cord. Silver preparations were made of the frontal, insular and temporal cortices, and basal ganglia. Senile plaques were not seen, but in the inferior temporal gyrus, moderately severe neurofibrillary changes of Alzheimer were noted. This was not noted in other parts of the brain examined. Celloidin preparations were made, and no evidence was found of demyelination gliosis, or overall loss of cells from the cortex. There was no evidence of arterial disease. It was concluded that the hydrocephalus was secondary to the presence of the tumour.

Comment.—In view of the papillœdema and moderately raised pressure at successive lumbar and ventricular punctures, the hydrocephalus was thought to be of the obstructive variety. However, as there was not incontrovertible evidence of an obstructive lesion on radiological grounds, it was felt that operation on the posterior fossa, which might have been purely exploratory, was not justified in a patient of this age. The normal lumbar cerebrospinal fluid protein did not support a diagnosis of acoustic neuroma. As the lesion could not be demonstrated, there were some observers who felt the hydrocephalus was possibly due to atrophy on the basis of cerebral arteriosclerosis (although the papillœdema could not be explained on this basis). This patient illustrates very well the progressive deterioration of mental function with unrelieved hydrocephalus. There also developed a spastic paraparesis, although to a lesser degree than in some other of our cases. The experiences with this patient, in whom age was the chief factor militating against operation, were partially responsible for reviewing the position in Case 7.

Case 7.—D. P. (M.V.H. 27689), female, aged 51. 8.9.52.

H.P.I.—7 years: isolated instance of vertigo. 6 years: progressive deafness of left ear with associated tinnitus for the first year of this period. 4 years: contraction of the left face, occurring many times each day, and extending over a period of eight months. Temporal and occipital headaches, increasing in severity and aggravated by head movements. 7 months: attacks of dazzling patterns of light in front of both eyes, lasting for as long as an hour, and occurring every second or third day for a period of a few weeks.

Examination.—Mental State: Euphoric. Intellect normal. Cranial Nerves: Deaf, left ear, otherwise normal. Limbs: Gait performed carefully, walking on a base a little wider than normal.

Investigations.—I.A.M.'s: Suggestion of erosion of left porus acousticus (*see*

fig. 3). L.P.: Pressure normal. Protein 80. A.E.G.: Moderate hydrocephalus, and a mid-line four ventricle displaced slightly backwards (*see* fig. 4). Myodil Ventriculogram: Free flow through ventricular system, though insufficient myodil was pooled in the fourth ventricle for good visualization of its floor and lateral recesses.

Diagnosis.—The clinical diagnosis was a left acoustic neuroma. As the erosion of the porus was only doubtful, as there was no obvious ventricular abnormality, and as the patient was relatively well, it was decided not to do an exploration at this stage.

Second admission three months later: Exploration again deferred.

Third admission fourteen months after the initial admission: There had been no change noted in her headaches and hearing, but her gait had become more unsteady, and, during the last five months, she had had eight "falling attacks." These came on without warning and were not associated with loss of consciousness. They were thought to indicate intermittent episodes of complete ventricular obstruction. She would suddenly feel giddy, her legs would give way, and she would fall, usually to the left side. In addition, she had noticed a deterioration in recent memory and a loss of interest in current events, and in the management of her home.

Examination.—Mental State: This had deteriorated. She was still euphoric and inclined to make facetious remarks. Not fully orientated, had difficulty with simple calculations, and tended to cover up mistakes and deficiencies by making jocular remarks. Cranial Nerves: As at first admission except for presence of ill-sustained nystagmus. Limbs: Gait broad based and unsteady, and she could not walk a line. Reflexes increased in left lower limb and clumsiness present at knee and ankle. Plantar responses flexor.

Investigations.—Audiometry: Complete deafness, left side. Caloric Test: Complete absence of left vestibular function. Ventriculogram: Slight increase in hydrocephalus. Possibly slight rotation of fourth ventricle to the right.

Diagnosis.—Acoustic neuroma.

Operation.—Exploration of posterior fossa. A typical acoustic neuroma was found. This was described as being "about the size of a small walnut," and "projecting up against the pons." The I.A.M. was quite large and the tumour was firmly adherent to it. A complete removal of the tumour was carried out.

She was seen eighteen months after the operation. At this time her mental state was normal and her gait excellent.

Comment.—The presentation in this case was unusual in that there was no history of cerebellar inco-ordination, and on examination, no involvement of fifth or seventh cranial nerves, no ataxy of movement at her first admission, and no papillœdema—in spite of a proven hydrocephalus. The main effect of the tumour in the 14 months' interval between admissions was on the mental state. The hydrocephalus, of course, remained unrelieved during this period.

Case 8.—*A. A.* (M.V.H. 29505), *male, aged* 69. 19.6.53.

H.P.I.—4 weeks: headaches, initially retro-orbital, and then bifrontal. They were discontinuous, not severe, and not associated with nausea or vomiting. 2 weeks: complaint of "woolly limbs" and short steps with staggering from side to side. Apathetic and disinterested during this period. 4-5 years: deaf in his left ear (on direct enquiry). Scant attention had been paid to this, and it had been attributed to a bicycle accident.

His wife confirmed the shortness of the history, and accentuated the mental side

of his illness. From being a jovial man, he had become apathetic and ill-looking, and had lost his appetite. His memory for recent events had deteriorated, and there was marked loss of interest in his surroundings. He ceased to take the usual care of his person, his habits deteriorated, and he became confused.

Examination.—Mental State: Confused, drowsy, unable to concentrate. Thought processes slow; very disinterested in the interview and examination. Cranial Nerves: Complete deafness, left ear, and minimal asymmetry left side of face. Limbs: Generalized slight weakness of all four limbs, with grasp reflexes, present bilaterally, and affecting fingers and toes. Slight but definite catatonia of upper limbs, and spastic lower limbs. All limbs clumsy, but there were no true cerebellar signs. Deep tendon reflexes uniformally depressed. Bilateral extensor plantar responses. Gait: broad based, with staggering from side to side. Balance: seriously affected. Tended to fall backwards, and to the right on eye closure.

Diagnosis.—In view of the short history of dementia and the presence of bilateral pyramidal and *extrapyramidal* signs with grasp reflexes, a provisional diagnosis of a corpus callosum tumour was made. It was decided to investigate him further by arteriography, but before this could be done he died of a massive pulmonary embolus.

Necropsy report.—A massive pulmonary embolus was present. In addition, examination of the brain revealed a small acoustic neuroma on the left side. This was about the size of a hazel nut and measured 18 × 7 × 8 mm. It had indented the brain-stem, and the fifth nerve was not involved (*see* fig. 5). On section, it had the characteristic histology of a neurofibroma. Serial horizontal sections of the brain revealed moderate dilatation of the lateral ventricles (*see* fig. 6). Detailed histological studies of celloidin and paraffin preparations of representative regions of the cerebral hemispheres, basal ganglia, corpus callosum, cerebellum and cord, did not reveal any evidence of loss of cells from the cortex, myelin degeneration or gliosis. There were very occasional areas of pallor around focally thickened blood vessels. There was no inflammation, the corpus callosum was not thinned, and there was no loss of Purkinje cells in the cerebellum. Silver preparations showed no plaques, and the neurofibrils appeared normal.

The conclusion drawn was that such changes as were present in the brain could be ascribed to internal hydrocephalus, due to pressure of the acoustic neuroma on the brain-stem.

Comment.—The clue to the correct diagnosis—unilateral deafness for five years—was only obtained on direct questioning. At the time it did not seem to fit in to the whole clinical picture. Little regard had been given to it by the patient. The absence of clinical involvement of the fifth and seventh cranial nerves, and of the cerebellum, is of interest, particularly so in the presence of marked involvement of the pons leading to hydrocephalus and bilateral change in the pyramidal and extrapyramidal pathways. The similarity to Case 12 in this last respect is worthy of note. The absence of papillœdema is also of interest.

Case 9.—N. F. (*L.H.* 40010/52), female, aged 58. 19.11.52.

H.P.I.—6 years: isolated attack of vertigo with vomiting. Since this episode, she tired easily, became disinterested, and gave up her job (as a private secretary). 4 months: episodes of blurred vision, each lasting for a few days. On D.Q.: deafness for several years, dating from some time during the war, when a bomb dropped near her.

Examination.—Mental State: Childish, giggles without cause. Agitated, verbose,

and jumpy. No defect of intellect or memory. Cranial Nerves: Bilateral papillœdema. V.A. right and left 6/18. Horizontal nystagmus. Minimal deafness right ear. Slight right lower facial weakness.

Investigations.—Skull X-ray: Evidence of raised intracranial pressure. Bilateral Arteriograms: Confirmed raised pressure. Ventriculography: Symmetrical hydrocephalus. Aqueduct poorly seen.

Diagnosis.—Prior to ventriculogram, mid-line lesion, probably colloid cyst. After ventriculogram, mid-line lesion posterior fossa tumour.

Operation.—Posterior fossa exploration. No tumour found. Decompressed.

Further course.—Readmitted after two months with first complaint of headache and sickness.

Examination.—In addition to previous findings, right corneal reflex absent, left diminished. Deafness more marked. B.C. greater than A.C. Slight ataxia right and left, more marked in lower limbs. Minimal weakness, right upper limb. Falling to right on standing.

Diagnosis.—Acoustic neuroma.

Further investigations.—Caloric Responses: Normal. Lumbar Puncture: Pressure 180. Protein 360. Myodil Ventriculography: Dilated fourth ventricle, pushed back but not tilted. Eroded porus revealed on these films.

Operation.—Large acoustic neuroma removed, extending far forward in front of pons. After follow-up fifteen months later she was very well.

Comment.—Atypical presentation with one attack of vertigo, peculiar behaviour, blurred vision, slight deafness ignored till late. It is interesting to note that a tumour of that size showed a peculiar affect disorder during most part of its growth, and then showed hydrocephalic symptoms and signs, with very little cerebellopontine disturbance till after the first operation. The caloric response on the affected side was normal. When last seen in June, 1954, she was very well, and there was no note of affect disorder.

Case 10.—*S. R.* (*L.H.* 11073/47), *male, aged* 34. 22.7.47.

H.P.I.—3 years: tinnitus in left ear. 7 months: severe vertical headaches, mostly at night. Few months: vomiting. 10 weeks: unsteadiness. Few weeks: mentally confused and drowsy. *No deafness or vertigo.*

Examination.—Bradycardia. Stiff neck. Suboccipital tenderness. Mental State: Fluctuating mental acuity, with inability to concentrate. Slow responses. Vacant expression, and disorientation. Cranial Nerves: Slight bilateral papillœdema. Horizontal nystagmus. Impaired upward conjugate movement and fixation of gaze. Very slight left deafness. Limbs: Slight left-sided cerebellar signs.

Investigations.—Lumbar Puncture: Pressure 300. Protein 10. Ventriculography: Gross symmetrical hydrocephalus. No filling of aqueduct or fourth ventricle.

Diagnosis.—Cerebellar neoplasm.

Operation.—Posterior fossa exploration. Cyst in left cerebellar hemisphere, tapped at 1 cm.

Further course.—Fluctuating consciousness. Repeat L.P. showed high pressure and protein 240. Two months after operation there had developed lead pipe rigidity in all limbs, with bilateral extensor plantar responses. No further signs of involvement of nerves in cerebellopontine angle.

Second operation.—Left acoustic neuroma removed.

Comment.—The symptoms of headaches, and mental slowing were

put down to hydrocephalus from a left cerebellar neoplasm because of papillœdema and left cerebellar signs; the tinnitus and the deafness found on examination only, were ignored in view of the rest of the picture. The protein of only 10 mg. made the diagnosis of an acoustic neuroma more difficult. Just before the second operation, he had developed brain-stem pressure and long tract signs, while no other cranial nerves, apart from the eighth, were involved.

Case 11.—*M. P.* (*L.H.* 21890/37), *female, aged* 51. 2.8.37.

H.P.I. (obtained mostly by direct enquiry from the daughter).—Many years: slightly deaf in the left ear, increasing in the last three years. Several years: headaches and nondescript neck pains. 2 years: occasional tinnitus. 15 months: (this was her major complaint). Attacks as follows: Sudden onset of a buzzing sensation spreading from the vertex backwards to the occiput. This resulted in a stiff neck for two to three minutes, and was followed by giddiness and a sensation of something coming down on her from above—immediately followed by a fall, in which she held her head and screamed with pain and became unconscious for a few minutes. On coming to, she complained of a smell like manure, lasting for two to three minutes. The duration of the whole episode sometimes lasted as long as thirty minutes. Convulsions and incontinence were not associated with these attacks, and they had increased in frequency to as many as three a day just before admission. 2 months: deteriorating vision, nearly blind in right eye; poor memory for recent events.

P.M.H.—No previous epileptic attacks.

F.H.—Nothing to suggest epilepsy.

Examination.—Mental State: Poor memory, especially for recent events. Confused, disorientated, euphoric. Inconsequential speech. Cranial Nerves: Bilateral papillœdema. V.A. right 6/6, left 6/12. Horizontal nystagmus; impaired upward and lateral conjugate deviation. Corneal reflexes absent on the left, impaired on the right. Sensation impaired on left side of face. Some wasting of muscles of mastication. Early left lower motor neurone facial palsy, incomplete left nerve deafness. Limbs: Minimal left cerebellar signs.

Investigations.—Skull X-ray: Evidence of increased intracranial pressure. Caloric Test: No response on left. Lumbar Puncture: Pressure 410. Protein 800.

Diagnosis.—Left acoustic neuroma.

Operation.—Partial removal of fair-sized tumour. The tentorium was pushed upwards by the tumour. There is no mention of herniation through the tentorial hiatus.

Comment.—The history of mental deterioration, and the attacks which appear more epileptic than vertiginous, without any other history except deafness to suggest any localization in the cerebellopontine angle, are features of interest in this case. However, the examination was more classical. The attacks are discussed in more detail later in the paper. Her mental state improved post-operatively to a great extent for a few months but later deteriorated, and she had to be certified. She died in March 1954, but no post-mortem was obtained.

In concluding this section, we should like to emphasize that 5 of our 6 patients with psychic changes had very little else *apart from deafness.*

The sixth patient (Case 11), had well marked signs of fifth and seventh cranial nerve involvement. So it becomes clear that unilateral deafness, far from being of little localizing value in the older patients, is the one (usually constant) feature which provides the clue to the correct diagnosis.

(D) *Combined Hydrocephalus and Brain-stem Pressure*

There are two important features presenting in a number of our cases, viz. motor manifestations and disturbances of consciousness, for which it has been difficult to assign a single cause. Accordingly, we have grouped them under this composite heading, not giving priority to either hydrocephalus or brain-stem pressure, in their causation, except where the evidence is definitely in favour of one or the other.

It is possible that hydrocephalus, ensuing after obstruction by the neuroma, is responsible for the motor manifestations in many cases. It is certainly true that at the time of admission, hydrocephalus was present in all except 1 patient with disorder of motor function.

During the natural history of growth of an acoustic neuroma, symptoms and signs due to pressure on the brain-stem are well recognized. Most authors follow Cushing in believing that such effects come on fairly late in the course of the disease, and definitely after involvement of other structures in the angle. Whilst this is true in the majority of cases, occasional tumours, whether large or small, growing close to the brain-stem, present primarily as problems suggestive of pontine, medullary, or midline neoplasms. Thus of the 8 patients discussed in this section, 3 had small tumours, 4 had large tumours, and in 1 the size is not stated. Tumours in such a position may not give rise to any cranial nerve disorder except that of the eighth, and not always that (for example, Case 12). It seems likely that the compression of the pyramidal and extrapyramidal pathways occurs in the pons—by direct, or indirect, pressure of the tumour exerted locally in the posterior fossa. The main effect of the pressure of the tumour on the brain-stem falls on the motor pathways.

Case 12.—*N. T.* (*M.V.H.* 27285), *female, aged* 70. 13.3.53.

H.P.I.—18 months: increasing weakness of the legs, which were stiff, and felt heavy to move. 6 months: Defective bladder control. Few months: Confined to the house and immediate neighbourhood. 12 months: Periodic headaches (direct enquiry). No history of memory disturbance, giddiness, defective balance or deafness.

Examination.—Mental State: Normal. Cranial Nerves: Normal. Limbs: Moderately severe spastic paraplegia, especially left, with extensor plantar responses. Tone increased in upper limbs but without loss of power.

Diagnosis.—Spinal paraplegia.

Investigations.—Lumbar Puncture: Pressure 210. Protein 350. A falx meningioma thus seemed likely and an air study was done. Ventriculography: Symmetrical hydrocephalus with dilatation of the third and fourth ventricles. The fourth ventricle appeared to be central. Myodil Ventriculography revealed slight displacement of the fourth ventricle to the right with some assymmetry of the lateral recesses (*see* fig. 7).

Operation.—Through a unilateral approach, a large left acoustic neuroma was removed. The acoustic porus was definitely enlarged as seen at operation.

Comment.—The difficulty in making a correct clinical diagnosis in this case is obvious. There was no suggestion of the features of the classical chronology of symptoms that we have come to associate with eighth nerve tumours. The complete absence of symptoms of involvement of structures in the cerebellopontine angle in the presence of a large tumour requires emphasis. The only symptom with a bearing on the correct diagnosis was headache, but even this was not a presenting complaint, being elicited on direct enquiry only. The main effect of the tumour was on the pyramidal pathway in the brain-stem. The presence of bladder disturbance is also noteworthy. The patient has since been seen two years following the operation, and there is no disturbance of equilibrium, weakness of lower limbs, or disorder of mental function.

Case 13.—*W. T.* (*L.H.* 13382/37), *male, aged* 53. 20.10.37.

H.P.I.—12 years: deafness of right ear began. 14 months: head injury. Unconscious for three hours. Uneventful recovery. Developed anosmia and fronto-occipital headaches. 12 months: weakness and dragging of the right foot. 8 months: staggering gait progressive. 7 months: mistiness of vision, began first in the right eye and then in the left. Few months: vertiginous attacks. Irritable, depressed and weepy.

Examination.—Mental State: Euphoria. Memory good on formal testing but poor for the main events of history. Cranial Nerves: Anosmia. Bilateral severe optic atrophy with blindness. Spontaneous lateral nystagmus. Impaired conjugate deviation to the right. Slight left lower facial weakness. Deaf, right ear. No fifth nerve palsy. Limbs: Left upper limb slightly spastic but with full power. Lower limbs spastic, slightly weak. Exaggerated deep reflexes. Left ankle clonus. Bilateral extensor plantar responses. No ataxia.

Investigations.—X-rays: Erosion of right petrous bone near I.A.M. Caloric Test: Right no response, left poor response. Lumbar Puncture: Pressure 360. Protein 80. Ventriculogram: Hydrocephalus, no filling of the fourth ventricle.

Diagnosis.—Right acoustic neuroma in spite of atypical features. Other alternatives raised were posterior fossa meningioma or cholesteatoma.

Operation.—Small acoustic neuroma removed, about 1 in. in diameter and situated more deeply than usual—towards the mid-line, nearer the basi occiput. "In such a situation it would be liable to produce more pontine compression and give a gross hydrocephalus."

Comment.—The presence of secondary optic atrophy and blindness in the absence of any neighbourhood signs, the absence of fifth and seventh nerve involvement, with sufficient pontine pressure to give spastic limbs and extensor plantar responses, are unusual features in the presence of a small tumour and no arachnoid cyst; the pyramidal signs can be explained on the hydrocephalus rather than direct pontine pressure. Also the fact that the petrous bone was eroded in the presence of a small tumour near the pons is interesting.

Motor manifestations.—Signs of involvement of the pyramidal pathway

in the brain-stem or at a higher level are well known in association with acoustic neuromas. Their frequency in the total series from which our cases are drawn is greater than our figures would indicate, as we have selected only those patients in whom the disorder was primary, or with or without other atypical manifestations, formed a presenting feature.

Symptoms of limb weakness were present in 4 cases. The case histories of 2 of these have been given above (Cases 12 and 13). In 3 of these, this weakness was due to pyramidal involvement, and in the other, was cerebellar in origin.

Signs of motor involvement as part of an atypical picture, were more common, being present in 11 cases. These varied between marked spastic pareses of lower limbs and increased reflexes with extensor plantar responses. Cases 12, 13, and 14, are the most important examples. Patient No. 12 when first seen in the out-patients' department, was thought to have a spinal paraplegia, as she exhibited a marked degree of spastic paraparesis which had been progressive over a period of eighteen months, and the signs in the upper limbs were much less marked. In this case it is unlikely that hydrocephalus was a factor over the whole period of eighteen months. There were no mental changes in this patient, and as she was 70 years old, it is probable that such changes would have been apparent had the hydrocephalus been of long standing. A prominent symptom in patient No. 13 was dragging of the right foot and examination revealed a spastic paraparesis, exaggerated reflexes in all four limbs, and extensor plantar responses, together with signs of increased intracranial pressure and deafness. There was some disorder of behaviour, also, in this patient. At operation the tumour was found to be "small (1 in. in diameter) and situated more deeply than usual—towards the mid-line, nearer the basiocciput. In such a situation, it would be liable to produce more pontine compression and give a hydrocephalus." Possibly hydrocephalus played the greater part in the production of motor symptoms but certainly the tumour was so situated as to produce direct compression of both pyramidal tracts. In Case 14, in whom pyramidal signs were present for nearly two years before the onset of signs of raised intracranial pressure, hydrocephalus cannot be invoked as a cause of the motor involvement.

Case 14.—*H. R.* (*L.H.* 39734/49), *female, aged* 38. 5.10.52.

H.P.I.—2 years: hissing noise in the right ear. 1 year: experienced a strange taste in her mouth, a numbness of the right half of the lower lip, and of the right temple.

Examination.—Mental State: Normal. Cranial Nerves: Doubtful pallor temporal half of left optic disc. Dissociated anæsthesia, right side of face. Limbs: Exaggerated deep reflexes. Bilateral extensor plantar responses. Trunk: Abdominal reflexes absent.

Investigations.—X-ray and L.P.: Normal findings.

Diagnosis.—Disseminated sclerosis.

Second admission, twenty-one months later: Symptoms unchanged until six

months prior to admission. 6 months: occasional attacks of vertigo. Increasing unsteadiness of gait. 2 months: diplopia on looking to the right. 2 weeks: hesitancy of micturition. Occasional morning headache.

Examination.—Mental State: Normal. Cranial Nerves: Horizontal and vertical nystagmus. Absent right corneal reflex. Dissociated anæsthesia right half of face—not so marked as at first admission. Slight deafness, right ear. Weakness of right palate. Limbs: Minimal ataxia right side. Reflexes exaggerated. Plantar responses extensor. Trunk: Abdominal reflexes absent.

Investigations.—Skull X-ray: Erosion of right I.A.M. Audiometry: Deafness to all frequencies right ear. Caloric Test: Response absent on right. L.P.: Pressure normal. Protein 130.

Diagnosis.—(1) Before investigations, intrapontine glioma. (2) After investigations, acoustic neuroma.

Operation.—Acoustic neuroma, the size of a golf ball, was removed.

Comment.—The onset with facial parasthesiæ and no deafness, with dissociated anæsthesia on face, and well marked pyramidal signs, was highly atypical and was suggestive of an intrapontine lesion, most likely disseminated sclerosis. When the symptoms had not cleared but advanced after three years and new physical signs which were still compatible with an intrapontine lesion had appeared, a pontine glioma or alternatively angioma was considered more likely. However, investigations showed the correct way. Early pyramidal signs in the absence of a hydrocephalus suggests local pressure on the pons; the bladder involvement, the early normal protein, and deafness only revealed by audiometry are other interesting features.

Case 15.—*A. L.* (*L.H.* 14272/47), *male, aged* 50. 6.1.49.

H.P.I.—3½ weeks: difficulty in shaving with the right arm. Tendency for the right leg to give way, and to fall to the right. These symptoms increased for a period of five days, and then improved. Deafness in right ear. 2 weeks: left frontal headache.

Examination.—Mental State: Low I.Q. Poor comprehension. Marked slurring dysarthria. Minimal dysphasia, according to one observer. Cranial Nerves: Horizontal nystagmus. Diminished right corneal reflex. Minimal right lower motor neurone facial weakness with loss of taste over anterior two-thirds of tongue. Right ear deaf. B.C. greater than A.C. Pharyngeal reflex absent. Defective sensation over right side of pharynx. Limbs: Right cerebellar signs. Weakness of right grip and equivocal right plantar response.

Investigations.—Lumbar Puncture: Pressure 180. Protein 110. Calorics: Diminished response on the right, indicating right vestibular nerve lesion.

Diagnosis.—Right acoustic neuroma.

Operation.—Removal of very large cystic tumour. Porus acousticus enlarged.

Comment.—A most unusual story, so short, and with so few local symptoms, yet showing a host of lower cranial nerve palsies. Facial sensibility was again spared in this case as in other cases, in spite of several other cranial nerves being involved; one wonders if the short history was not due to the largely cystic nature of the tumour.

In addition, Cases 6, 8, 10, and 17, each had definite spastic paraparesis

with pyramidal signs of varying degrees in all four limbs. In Cases 8 and 12, in addition to the pyramidal signs, there was marked increase in tone in the upper limbs of the extrapyramidal variety, leading to a tendency to catatonia, very marked in Case 8, in whom bilateral grasp reflexes were well developed, and slight in Case 12. Most of these cases have already been given; that of 17 follows:

Case 17.—*H. S.* (*L.H. Chase Farm*), *male, aged* 35. 2.10.37.

H.P.I.—3-4 years: frontal headaches. 3 years: attacks of a "black spot" in front of his right eye every time he stooped. This progressed to severe visual failure in the right eye, followed by the left eye. 1 year: (on D.Q.). Unsteadiness of gait. Had one attack of giddiness with sweating, followed by loss of consciousness for one minute at the beginning of this year. A second attack occurred two months later. This was associated with a fall but not loss of consciousness. 1 month: two attacks of peculiarly vivid memories of smells lasting a few minutes each. 3 years: (on D.Q.). Progressive deafness, left ear.

P.M.H.—No attacks to suggest epilepsy.

F.H.—Nothing to suggest epilepsy.

Examination.—Mental State: Slight defect of memory. Cranial Nerves: Bilateral papillœdema with secondary atrophy. V.A. right 6/18, left hand movements only. Right pupil more sluggish than left. Impaired conjugate deviation to the left and upwards. Nystagmus. Corneal reflex slightly diminished on the left. Gross wasting and weakness of muscles of mastication on the left side. Severe deafness left ear. Limbs: Hypotonia, tremor and ataxia of left upper, tremor of right upper; spasticity of both lower limbs, with exaggerated reflexes. Right plantar response equivocal. Ataxia of the left lower limb.

Investigations.—Skull: Signs of increased intracranial pressure. Caloric Test: Responses absent on the left.

Diagnosis.—Acoustic neuroma.

Operation.—Partial removal of very large acoustic neuroma which was adherent to, and abutted firmly against the tentorium, pushing it upwards.

Comment.—The chronological order of symptoms, with very early eye symptoms was quite atypical; the physical signs were suggestive of an angle tumour, probably an acoustic neuroma, but severe weakness and wasting of the masticatory muscles, with very little sensory involvement and sparing of the seventh cranial nerve with well marked signs of brain-stem pressure is interesting especially with a massive tumour. The coarse tremors, worse in the upper limb, are difficult to explain but might be due to involvement of the red nucleus. The uncinate attacks can be explained on the basis of the upward extension of the tumour.

It has been shown that extrapyramidal rigidity and catatonia can both be manifestations of brain-stem involvement without rise of intracranial pressure (Holmes 1952). We feel that in our older age group—especially Case 12—the pyramidal and extrapyramidal signs were probably due to injury to these tracts within the brain-stem. It is possible that this is the result of direct pressure of the tumour; but it is more likely due to the factor of vascular disturbance in the brain-stem, associated with a tumour in the posterior fossa of an old person. This vascular disturbance may

take the form of pressure or traction by the tumour on vessels leading to impairment of the blood supply. It will be interesting to study the occasional patient with an acoustic neuroma who dies without operation for possible changes in the blood supply to the brain-stem which may have occurred in the presence of the tumour.

Mills and Weisenberg (1905) reported a case of "fibromatous tumour of the acoustic neuroma," presenting with gross spastic paraplegia, mental confusion, and disintegration of personality, with double incontinence. The diagnosis was made at autopsy, and Mills stated in retrospect that had he paid more attention to the minimal deafness and some history of paræsthesia on the face, he would have made a correct diagnosis during life (*this, in spite of the absence of any cerebellopontine angle signs except deafness*—our italics). It is of interest to recall that Mills' statement was made some twelve years before Cushing formulated the syndrome which has since become classical. The above case had gross hydrocephalus, although the authors held the opinion that the paraplegia was probably due to brain-stem involvement.

We have already mentioned that the occurrence of motor manifestations is well recognized as a late part of the fully developed cerebellopontine angle syndrome. Its repetition now serves to emphasize that in some cases, particularly amongst the older patients, motor symptoms and signs may be present with an incompletely developed syndrome. Deafness alone may be present to indicate the correct localization; or deafness, with mental and personality changes. If deafness is not detected, or disregarded, there is real danger of making a diagnosis of progressive atrophy, due to cerebrovascular degeneration, and so failing to make further investigation.

Disturbances of consciousness.—The tonic cerebellar seizures which occur in the very late stages of the development of the cerebellopontine angle syndrome are possibly due to sudden increases in the intracranial pressure associated with a "pressure cone." It is possible that direct pontine pressure by the tumour, with fluctuations in the blood supply to the brain-stem, is responsible for these seizures. These have been very well described and discussed by previous writers. Usually by the time that they occur, there is little difficulty in arriving at a diagnosis. We do not have an example of this type of attack in our own material. The attacks that did occur will now be described, and possible mechanisms discussed.

Disturbances of consciousness occurred in 6 of our Cases (1, 6, 7, 11, 16, and 17). All except Case 16 have been presented. The report on Case 16 now follows:

Case 16.—*C. F.* (*L.H. P.P.*), *female, aged* 47. 20.3.43.

H.P.I.—2 to 3 years: right-sided deafness, rushing noises both ears. 3 months: several falls, with giddiness, consisting of a "sinking feeling," without sense of rotation. 2 months: frontal and occipital headaches. Few weeks: diplopia and

blurred vision. 5 days: several epileptic attacks with typical cry, twitching of right face and leg, and unconsciousness.

P.M.H.—Nothing to suggest epilepsy.

F.H.—Nothing to suggest epilepsy.

Examination.—Cranial Nerves: Bilateral papillœdema. Horizontal nystagmus. Early right lower motor neurone seventh nerve palsy. Total deafness right ear. Limbs: Bilateral cerebellar signs, right more than left.

Investigations.—Skull X-ray: Eroded porus right side. Caloric Test: No response right side. Lumbar Puncture: Pressure 340. Protein 220.

Diagnosis.—Right acoustic neuroma.

Operation.—Relatively small neuroma removed, 1 in. vertically, but bigger from side to side—"from the feel of the tumour when I was removing it, I think it may have been wedged up into the opening of the tentorium."

Comment.—The history and mode of progression of the disease were somewhat atypical. The physical signs were more in keeping with the classical description, although the fifth nerve was spared. The diagnosis was made clinically, and was supported by other investigations. The short history, the falling attacks without unconsciousness or true vertigo, and the focal epileptic attacks were highly atypical. The patient died post-operatively from brain-stem softening. Apart from the probable extension of the tumour into the tentorial hiatus, there were no macroscopic abnormalities recorded to explain the focal attacks; no microscopic sections of the cerebrum available.

In Case 6, the episodes occurred only after an air encephalogram. There were no convulsive seizures or other features to suggest a cerebral cortical or subcortical initiation of these attacks. Tonic movements of the limbs did not occur. Nevertheless, it seems likely that they were either due to pressure of the tumour on the brain-stem, or to the associated hydrocephalus.

Patient No. 7, during five months prior to her second admission, had eight falling attacks. These occurred without warning, and consciousness was not lost during them. Each attack started with a sudden feeling of giddiness, her legs then gave way, and she fell, usually to the side. In Case 1 a single fit occurred eight years before admission. Patient No. 16 had a series of focal, motor, Jacksonian seizures five days before admission. Each fit was ushered in by a cry. She then fell to the ground, with twitching of the right leg, and spasm of the right side of the face. She became unconscious and remained so for several minutes. The autopsy on this patient did not reveal any separate intrinsic cerebral lesion to account for her attacks. However, in addition to hydrocephalus, there was possible wedging of the tumour in the tentorial hiatus.

In Case 11, there was a four-year history of most odd attacks. These were a presenting feature, and each consisted of a buzzing sensation accompanied by severe vertigo and headache, followed by unconsciousness, and on awakening, an olfactory hallucination of a foul smell. There were

two attacks of sudden falling in Case 17, one with loss of consciousness, in the year preceding admission. In the month before admission she had two sudden episodes of "peculiar vivid memories of smells," each lasting for a few minutes.

None of the above patients gave a history of previous epileptic attacks, and in none was there a family history of epilepsy. There was no recurrence of the seizures in Case 11 following removal of the acoustic neuroma during the follow-up period of six months. Patient No. 7 had no further falling attacks when seen eighteen months after her operation.

None of the above episodes was of the type described as "tonic cerebellar fits." These were well described by Cushing (1917) and by previous authors. Disorders of consciousness with space occupying lesions in the posterior fossa have been well recognized for many years. Mills (1905) stated that whilst attacks of opisthotonus, tonic spasms, and generalized rigidity were observed by him in several cases of cerebellar tumours extending forward into the angle, and also producing hydrocephalus, he had also seen convulsions, "unilateral and generalized, but more commonly the latter, with unconsciousness, in a considerable percentage of cases of cerebellar tumour under his care which had produced ponto-oblongatal pressure symptoms." He described 1 patient with a posterior fossa tumour who had attacks starting with a high-pitched tinnitus suddenly increasing in intensity, followed by objective vertigo, with or without forced movements, and then dropping to the ground. At times, these attacks were associated with momentary blindness and loss of consciousness. Similar attacks were noticed in several other cases, especially in elderly people, and Dana (1905) believed the mechanism to be a cerebellar or brain-stem disturbance, following a temporary cutting off of the blood supply to the brain-stem. He did not think they were due to labyrinthine vertigo, and he stated that in his own experience, and that of other writers, this particular cerebellar syndrome was not infrequent. Cushing describes epileptic attacks in two of his cases (10 and 29).

Cairns in his Victor Horsley lecture on "Disorders of Consciousness with Lesions of the Brain-Stem and Diencephalon" (1952) described several kinds of attack of unconsciousness occurring with lesions disturbing the brain-stem mechanism. He took great care to point out that it is not necessary to have hydrocephalus with a posterior fossa lesion to produce disorders of consciousness, either prolonged or in attacks. Indeed, he felt that direct involvement of the brain-stem by an intrinsic or extrinsic tumour process was responsible for the unconscious episodes. In lesions outside the posterior fossa causing prolonged or temporary attacks of unconsciousness, the distortion of the brain-stem by the secondary pressure cone from the raised intracranial pressure, was thought to be a basis of these attacks, and not disturbance of cerebral function. Amongst the types of attacks, he mentioned such temporary episodes as

tonic fits, minor epilepsy, resulting in falls or "drop attacks," and two posterior fossa post-operative cases with series of generalized convulsions for which no adequate explanation could be found. The following is a quotation from this paper: "I conclude from this comparison that the disturbance of consciousness with lower brain-stem tumours, can be mainly ascribed to involvement of the brain-stem, even when there is rise of intracranial pressure. And indeed, it is probable that most episodes of unconsciousness in cerebellar tumours are due to encroachment upon the brain-stem as a result of pressure cones."

Recent experimental work on monkeys and cats (French and Magoun, 1952, French, von Amerongen, and Magoun, 1952) has established the presence of a medial system of afferent conducting pathways in the brain-stem, hypothalamus and subthalamic region. This system is situated within the central reticular formation, and is distinct from the laterally situated sensory tracts (medial and lateral lemnisci). This medial system receives an afferent inflow from the lateral tracts, but within it there is no organization of sensation into discrete modalities, and there are association pathways between it and the cerebral cortex, particularly of the pre-motor frontal areas. This system is concerned with the arousal reaction in cats and with activation of consciousness and alertness in monkeys; these responses are produced when it is stimulated either by incoming afferent stimuli or electrically. Destructive lesions within it produce states simulating unconsciousness in humans—which is sometimes prolonged. In man, states of prolonged alteration in "unconsciousness" have been described with central brain-stem lesions, with special reference to the "activating system" of the central reticular formation (French, 1952). It is tempting to suggest that involvement of this formation may at times be transient and responsible for some cases in which alterations of consciousness occur, in association with acoustic neuroma.

It will be clear from our own records, and that of others, that occasionally in patients with acoustic neuroma, there may be associated either early or late in the history, disturbances of consciousness. These may, or may not, conform to the classical description but are doubtless part of the symptomatology. They are due in some cases to the direct effect of the tumour on the cerebellum or brain-stem, or by its remote effect on the temporal and frontal lobes, following hydrocephalus and elevation of the intracranial pressure. However, in other cases there is a more direct relationship between the tumour in the posterior fossa and the temporal lobe. This was so in Cases 11, 16, and 17. In these, where focal or generalized epileptic attacks occurred, a close relationship was found between the tumour and the tentorium and hiatus. The attacks in Cases 11 and 17 were uncinate in character as might be expected from a direct or indirect effect on the medial structures in the temporal lobe.

(E) *Brain-stem Pressure*

In addition to the role that this process plays in the production of motor symptoms and disturbances of consciousness, there is one group of signs in which it is almost certainly solely responsible, i.e. *defects of conjugate deviation of the eyes.* Impairment or loss of conjugate deviation of the eyes indicates involvement of the upper brain-stem by an intrinsic or extrinisic lesion. This sign was present fairly early in the disorder, in 6 of our patients (Cases 5, 10, 11, 13, 17, and 18). It was present as an early manifestation of brain-stem involvement, and before the development of fifth and seventh cranial nerve signs.

(F) *Involvement of Other Structures in the Angle*

(1) *Facial Nerve:* There was no complaint of facial weakness amongst the patients in this group. 2 (Cases 12 and 17) had twitching of the facial muscles (bilaterally in Case 17). Only 3 patients had definite lower motor neurone weakness (Cases 4, 11, and 16). It was slight in all 3. A facial asymmetry was noted in 3 other patients.

(2) *Trigeminal Nerve:* Only 1 patient (Case 14) complained of sensory symptoms in the face—this was a presenting symptom, there being no deafness. 10 patients had *normal corneal sensation;* in 8 it was reduced. Of these 8, 3 (1, 9, and 14) developed this sign very late, 2 at admission, and 1 after several investigations had almost established the diagnosis. Only 2 patients (14 and 17) had impairment of superficial sensibility over the face. In patient No. 14, there was dissociation of sensory loss, which led to a diagnosis of an intra- rather than extra-pontine lesion. In this case, depression of the corneal reflex was not present until two years later. In Case 11, there was gross unilateral motor weakness of the fifth, with a depressed corneal reflex but no sensory loss.

Depression of the corneal reflex as a positive sign is of great value. *When absent a firm conclusion cannot be drawn.* It should be noted that the corneal reflexes were normal in 4 of the 6 patients, with psychic changes (Cases 7, 8, 9, and 10), and only questionably impaired in Case 6. In these patients, the tumours had been present for many years, and yet trigeminal manifestations, which normally occur fairly early, had not developed.

Diplopia and sixth nerve palsy.—These occur late in the disease, and are not of localizing significance. In Case 2, diplopia was the first symptom, but disappeared within a month of its onset. 5 patients complained of double vision, but only 2 had a sixth nerve palsy, and then only on admission.

Dysarthria and dysphagia.—There was no complaint of either disturbance amongst the patients in this series. 2 patients (4 and 15) had impaired pharyngeal reflexes. In patient No. 15, taste was impaired over the whole of one side of the tongue.

Imbalance and ataxia.—This formed a presenting feature in 1 patient

only (Case 4). In 10 others there was a history of unsteadiness or poor balance at varying times in the story. The symptom was marked in 5, slight in 4 (1 at readmission) and occurred at night only, in 1.

On examination, 13 patients were found to be ataxic, 8 only slightly so (2, Cases 9 and 10, at readmission only). In 7 patients, the ataxia was bilateral, being more marked on the side of the tumour. In our series, the cerebellar involvement had no definite chronology.

Length of history.—In the average case, this is about four years in most of the published series. In Edwards' and Patterson's cases, a mean period of 3·8 years elapsed between the first symptom and admission to hospital. These authors found that symptoms other than those related to the auditory nerve, are present for about half of this period. However, they do stress that in a small group of cases, all the symptoms, excluding deafness, occur over a short period of time.

In 5 of our patients (2, 4, 10, 15, and 18), the history ranged from three months to one year. In patient No. 15, the total history was one year, but if mild periodic tinnitus be excluded, then only three and a half weeks elapsed between the next symptom, and admission to hospital. In 5 patients (1, 5, 8, 13, and 16), deafness, though present for several years, had been ignored or regarded as insignificant, and required to be elicited by direct enquiry. The remaining symptoms in these cases were all less than one year in duration.

So, excluding the auditory symptoms, 10 of the 18 patients gave a history of less than one year. It was of interest, too, that patients with short histories were much younger on the average (42 years) than those with long histories (52·3 years). In the group of 6 patients, in which mental symptoms were prominent, the average length of the histories was five years and the average of the patients comprising this group was fifty-five years.

In conclusion, the duration of the history, regarded alone, may mislead rather than clarify the position if the clinician is expecting a long history developing along the lines of the usual chronology. This is particularly true of those cases where other features of the natural history are also atypical.

Investigations.—The following investigations may contribute to a diagnosis of acoustic neuroma, and particularly in an unusual case where the clinical features are atypical.

(1) *Lumbar puncture:* An accurate measurement of the intracranial pressure may be obtained on lumbar puncture. An elevation of the protein content may occur but is also found in other types of tumour which are in contact with the cerebrospinal fluid pathways. In our own patients, the protein was elevated in 12, normal in 3, and not recorded in 3 (in these, lumbar puncture was not done in 2 because of very marked

papillœdema, and in 1 patient (Case 8) because the death of the patient from pulmonary embolus cut short the investigations).

(2) *X-ray of skull and internal auditory meatus:* The meatus is enlarged in a relatively high proportion of patients with acoustic neuroma. Lundborg (1952) stated that plain X-rays were definitely positive in 63·2 per cent of cases. Bull (1953) found that in 75 per cent of 50 cases, the internal auditory meatus was widened. This latter author, in reference to the place of plain radiography of the skull in posterior fossa tumour cases, states that "*never* should plain X-rays be omitted from the general preliminary examination." He goes on to say: "I must stress this because one has heard it said that the diagnosis of acoustic neuroma, for example, is sometimes so obvious clinically, that plain X-rays are redundant. Such teaching is most dangerous, and sooner or later leads to an error in diagnosis."

In our own patients, the internal auditory meatus was X-rayed as a separate investigation in 6. In 4 of these, erosion was present. It is interesting that there is no note of this examination in 12 of the cases. The absence of erosion should not be allowed too much weight in a patient who is in other respects atypical. We have referred earlier to tumours which arise from the medial part of the auditory nerve. These cannot be expected to erode the meatus in the early stages. This point has been mentioned by Bull (1953), who states: "Plain X-rays will *never* be able to give the key to the diagnosis of all acoustic tumours for some are so centrally situated that they do not erode the meatus, and a few others are too small to widen the meatus."

(3) *Audiometry and caloric test:* The otological assessment of any patient suspected of having an acoustic neuroma is of fundamental importance. Further, the otologist's help should be enlisted in patients with intracranial tumours, especially those of the posterior fossa, where the clinical picture is bizarre and the diagnosis not clear. Audiometry was carried out in 3 of our cases and revealed a conductive deafness in all.

The old criteria of audiometric examination indicate whether deafness is perceptive or not, but do not give information as to which particular component of the perceptive mechanism is affected. During the last fifteen years there have been refinements in the technique of audiometry allowing, as Dix, Hallpike, and Hood (1949) have stated, the development of "new criteria for nerve deafness." These are (1) the loudness recruitment test and (2) the intelligibility test for amplified speech. These help in the differential diagnosis between Ménière's disease and eighth nerve tumour. In the tumour cases there is degeneration of the spiral ganglion but not of the organ of Corti. This latter structure is as a rule affected in Ménière's disease. It is this change, when present, which accounts for deafness in Ménière's disease persisting between acute attacks. Tuning-

fork tests reveal identical results in both diseases and do not help in differential diagnosis.

In Ménière's disease, loudness recruitment is always present, is complete and over-recruitment sometimes occurs. In eighth nerve tumour, loudness recruitment does not occur. In the intelligibility test for amplified speech, the results are in the opposite sense, that is, in a patient with eighth nerve tumour, the curve of intelligibility may be absent. These tests were referred to by Elliott and McKissock (1954) in a paper on the early diagnosis of acoustic neuroma. Their use is recommended in all patients suspected of having intracranial tumour in whom any suggestion of deafness occurs, or in whom a posterior fossa localisation is being considered.

The caloric test was done in 13 of our patients. In 10, a diminished or absent response on the side of the tumour was demonstrated, and a correct diagnosis made in 6. The caloric responses were *normal* in 3 *patients*. In 1 of these (Case 1) audiometry revealed a hearing loss to all frequencies. Lundborg (1952), in an analysis of 300 of Olivecrona's cases, pointed out that the caloric responses were normal in 15·8 per cent. Audiometry was performed in 23 cases only of this large series, but Revilla (1947), who performed the test on all his 145 cases, found a total deafness in 107, and a partial deafness in 32. In only 5, was normal hearing retained.

(4) *Ventriculography:* This was carried out in 9 of our patients. In all but 1 of these 9, the diagnosis before ventriculography was in doubt. An obstructive hydrocephalus was revealed in all. In patient 6 throughout, and in patient 7 at the first admission, there was no clear evidence of the lesion responsible for the obstruction. In some cases, the aqueduct and fourth ventricle were not well shown in the air study. In such cases positive contrast ventriculography with myodil may aid in demonstrating these two structures, but in 1 of our cases, there still remained a doubt even after this investigation had been performed.

Where a confident diagnosis of an acoustic tumour was made in our series, a ventriculogram was not done. This is in accord with the view held by many neurosurgeons that the investigation is unnecessary when the diagnosis is clear. However, some neurosurgeons advise ventriculography in all cases of posterior fossa tumour.

(5) *Air encephalography:* This was carried out in 3 of our cases. In the absence of clinical evidence of hydrocephalus, it is relatively free from risk. Even with slight degrees of increased intracranial pressure it can be employed. Smaller amounts of air are required to give good views of the aqueduct, fourth ventricle, and cerebellopontine angle cisterns than with ventriculography. The technique of demonstrating these cisterns has been described by Robertson (1946) and Lindgren (1950).

We feel that there should be little hesitation in employing one or all

of these special investigations in the atypical case of posterior fossa tumour, when an acoustic neuroma may be brought to light.

Diagnosis.—The establishment of a correct diagnosis of an acoustic neuroma may be very difficult as study of the case reports will have shown. On the basis of the history and examination, a correct diagnosis was made in 6 of our patients. The following list includes most of the different diagnoses considered in the other 12—colloid cyst of the third ventricle, fourth ventricle tumour, cerebellar glioma and hæmangioblastoma; sphenoidal ridge meningioma; disseminated sclerosis, pontine glioma, pontine angioma; spinal paraplegia, falx meningioma and corpus callosum glioma. The difficulties in arriving at a correct diagnosis are well brought out in the following case report:

Case 18.—*C. C.* (*L.H. Chase Farm*), *male, aged* 28. 21.10.42.

H.P.I.—3 months: severe left frontal headache. 2 months: diplopia, unsteady gait, vertigo, occipital headache. 2 weeks: deafness and tinnitus, left ear.

Examination.—This patient was seen as an outpatient by the late Dr. Riddoch, who found no signs of raised intracranial pressure, and made the comment "probably pontine disseminated sclerosis but the symptoms have persisted long without improvement." Then ten days after this examination the following signs were present: Cranial Nerves: Early papillœdema. Bilateral ptosis, right more than left. Bilateral proptosis. Nystagmus. Impaired conjugate deviation to the left. Diminished left corneal reflex. Early left lower motor neurone facial weakness. Moderate deafness left ear. B.C. greater than A.C. Limbs: Slight ataxia left lower limb.

Investigations.—Lumbar Puncture: Pressure 240. Protein 100. Caloric Test: No response left ear.

Diagnosis.—(1) As an outpatient, pontine disseminated sclerosis. (2) Possible fourth ventricular tumour. (3) Following operation, pontine tumour. (4) (After 3rd admission): High vermis tumour or cystic hæmangioblastoma.

Operation.—Posterior fossa exploration with decompression. Indefinite resistance in left cerebellar hemisphere felt at 2 cm.

Further course.—Gradual improvement. X-ray therapy given on the grounds that this might be a pontine tumour.

2*nd Admission* 3 *months later:* Deafness had increased and a left sixth nerve palsy had developed.

3*rd Admission* 3 *months later* (6 months from initial admission): Headache less.

Examination.—Left fifth, sixth, and seventh palsies much less marked.

Diagnosis.—In view of improvement in cranial nerve palsies, pontine tumour did not seem likely, and high vermis tumour spreading to the left side, or a cystic hæmangioblastoma seemed much more likely.

Second operation.—Re-exploration with removal of large acoustic neuroma.

Comment.—The early rapid history and physical signs, with the possible exception of headache, would fit in well with pontine disseminated sclerosis. The subsequent developments suggested a pontine or fourth ventricle tumour. However, with improvement on deep X-rayed therapy and decompression, that diagnosis was discarded in favour of a high vermis tumour or cerebellar hæmangioblastoma. The early eighth cranial nerve involvement with an inactive labyrinth may have been a clue, but on account

of the onset and progression of the condition, one could hardly be expected to diagnose an acoustic neuroma. It is interesting that the facial sensation was not impaired when so many structures in the angle were involved. A ventriculogram might have helped in establishing the diagnosis earlier.

Summary and Conclusions

(1) A substantial proportion of patients with unilateral acoustic neuroma have features which are atypical in that they depart from the usually accepted standards.

(2) In our own material, this proportion has been 22½ per cent.

(3) The main reason for this difference in presentation is the occurrence of tumours having a medial site of origin as compared with the greater proportion of tumours which arise laterally, i.e. within the meatus.

(4) Tumours arising at this site are conveniently placed to produce their effects in one or more of the following ways:

(*a*) By the establishment of hydrocephalus.
(*b*) By direct pressure on the brain-stem.
(*c*) By disturbances of the blood supply to the brain-stem.

(5) Hydrocephalus is manifest either in a dramatic fashion when arising acutely, or slowly and insidiously when it is of long standing. The main effects of acute hydrocephalus are the production of an intermittent block and rapid deterioration of vision; those of the chronic condition, mental changes and motor manifestations.

(6) The acute hydrocephalic symptoms would appear to be associated with larger tumours occurring in the younger age groups; whereas the manifestations of chronic hydrocephalus are in the older age groups and are often associated with small tumours.

(7) The occurrence of disorders of consciousness (including epilepsy) in patients with posterior fossa tumours is worthy of emphasis.

(8) Deafness. This is the single feature which in the great majority of cases remains typical and is such an invaluable sign in localization. Its importance cannot be overstressed.

(9) Cushing's clarification of the cerebellopontine angle syndrome was the major factor in focusing the attention of clinicians on the tumours causing it, in particular, the acoustic neuromas. The chronological syndrome so formulated remains the greatest help in arriving at a diagnosis in most patients harbouring these tumours. However, now that radiological and otological aids are available, it should be possible to make the diagnosis in a further group of patients in whom the syndrome is incompletely developed, or the clinical picture altogether atypical.

Acknowledgements

We are grateful to Sir Russell Brain for permission to report on patient

No. 8, and on those patients admitted under his care at the London Hospital. We wish to express our thanks to Dr. Nevin and Dr. Dimsdale for permission to report on their patients admitted to the Maida Vale Hospital. We have pleasure in thanking Mr. Valentine Logue for putting at our disposal the surgical notes of Cases 6, 7, and 12, and for helpful advice and criticism during the preparation of this paper.

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LEGENDS FOR PLATES

PLATE XVI

FIG. 1 (*Case* 6).—Base of brain with tumour in situ. Note deformation of pons and medulla. A small portion of the tumour has been removed for histological examination.

PLATE XVII

FIG. 2 (*Case* 6).—Coronal section of brain to show degree of hydrocephalus.

FIG. 3 (*Case* 7).—X-ray showing erosion of left internal auditory meatus. A few droplets of myodil are present.

PLATE XVIII

FIG. 4 (*Case* 7).—Ventriculogram revealing a moderately severe degree of hydrocephalus.

FIG. 5 (*Case* 8).—Base of brain with small acoustic neuroma in situ. Slight deformation of pons is shown.

PLATE XIX

FIG. 6 (*Case* 8).—Horizontal section of brain demonstrating a moderate degree of hydrocephalus.

FIG. 7 (*Case* 12).—Myodil ventriculogram showing displacement of fourth ventricle to the right.

PLATE XVI

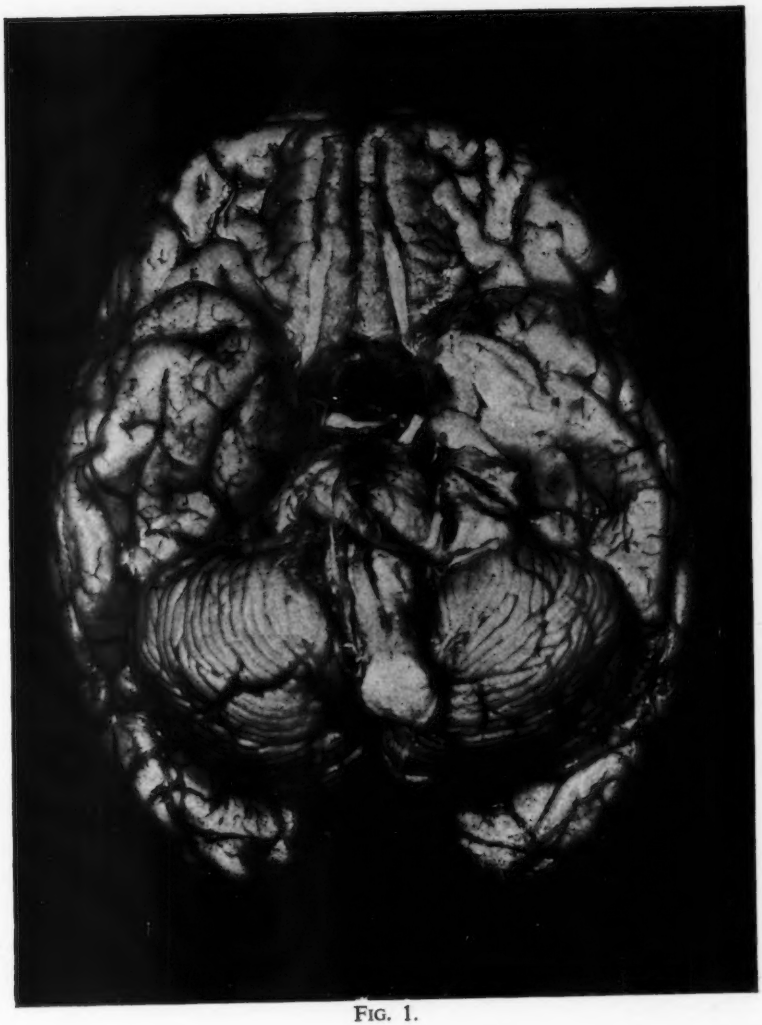

FIG. 1.

To illustrate article by R. H. Shephard and N. H. Wadia.

PLATE XVII

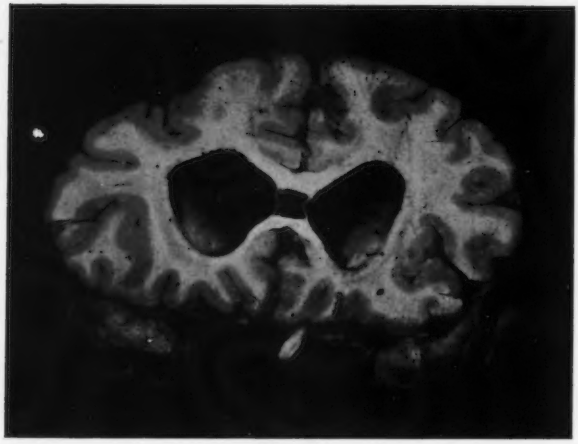

FIG. 2.

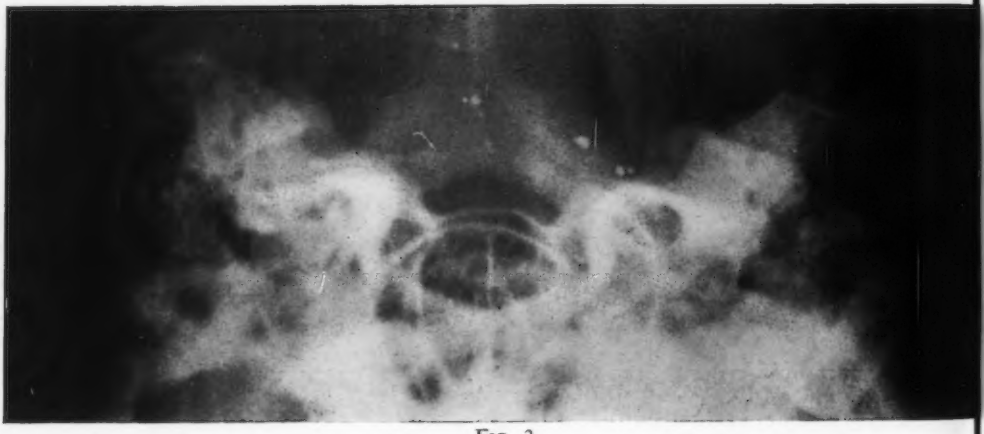

FIG. 3.

To illustrate article by R. H. Shephard and N. H. Wadia.

FIG. 4.

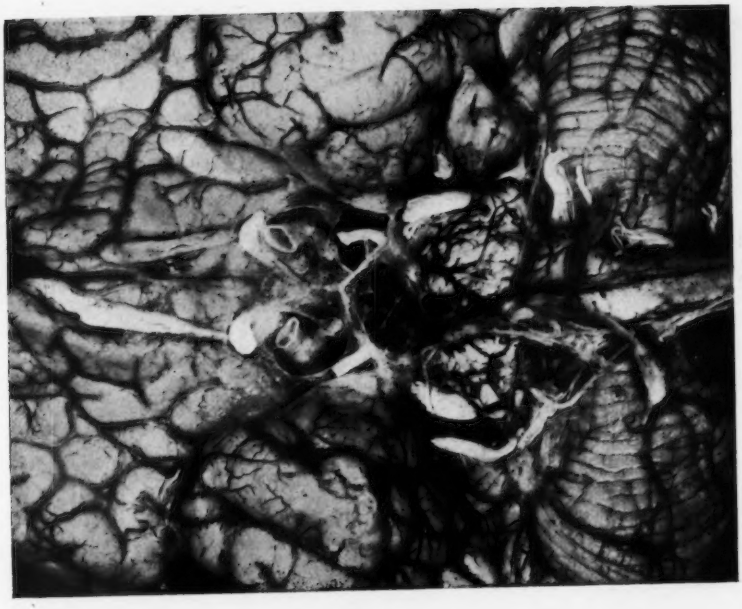

FIG. 5.

To illustrate article by R. H. Shephard and N. H. Wadia.

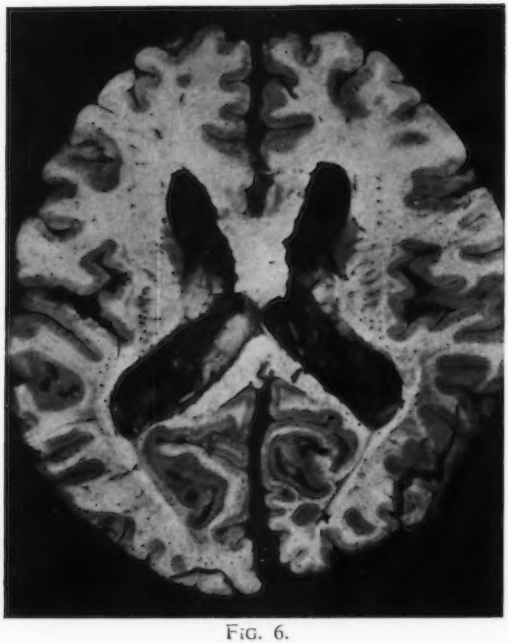

FIG. 6.

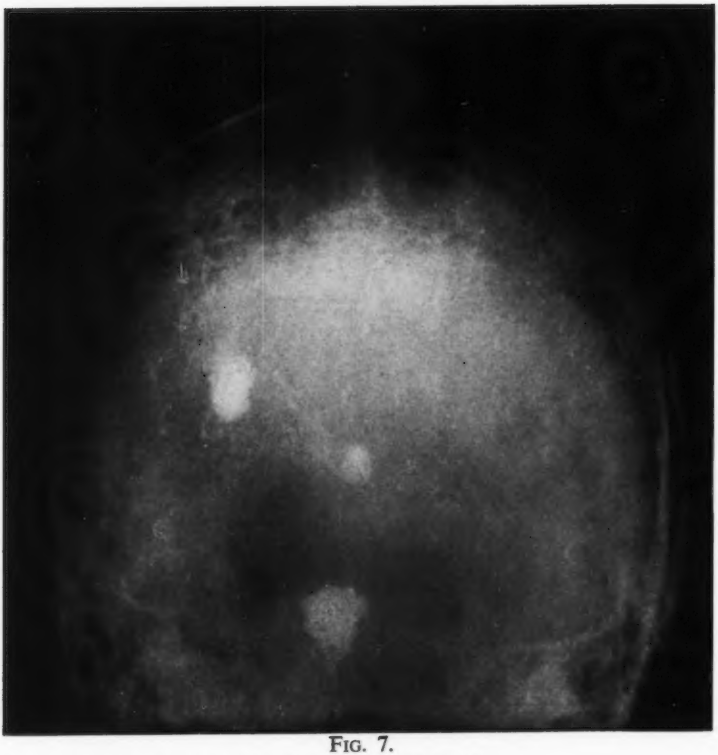

FIG. 7.

To illustrate article by R. H. Shephard and N. H. Wadia.

THE CERVICAL PORTION OF THE VERTEBRAL ARTERY A CLINICO-PATHOLOGICAL STUDY

BY

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INTRODUCTION

MUCH valuable information has been gained in the past from anatomical studies of both the basilar and vertebral arteries and their terminal branches. All neurologists, when concerned with the localization of vascular lesions within the brain-stem, would acknowledge the debt they owe to such anatomical studies as those of Stopford (1916) and Foix and Hillemand (1926). Nevertheless, in the case of the vertebral artery, continued attention to its anatomical distribution has tended to overshadow what is an equally important function of the artery; the provision of a collateral channel of blood supply via the Circle of Willis to the brain as a whole.

The importance of atheroma of the cervical portion of the carotid artery escaped recognition for many years and it is not surprising, therefore, when one considers the anatomical course of the vertebral artery within the neck, that it too has suffered a similar neglect. Examination of the vertebral artery at routine necropsy is usually confined to the terminal intradural portion of the artery, since examination of the major part of the vessel within the vertebral canal is both time-consuming and technically difficult. But recent recognition of the frequency and importance of internal carotid artery occlusion as a cause of cerebrovascular lesions has focused attention sharply on the collateral circulation and it is as part of this compensatory system that the vertebral artery must assume considerable importance.

In the published studies on carotid artery occlusion no mention is made of the condition of the cervical portion of the vertebral artery. Yet if the vertebral artery in the cervical portion should be as liable to atheroma as the carotid, then knowledge of the degree and extent of the lesions would be of considerable importance in the pathological interpretation of the clinical picture. To investigate this point we have carried out a clinical and pathological study on a series of patients admitted to the Manchester Royal Infirmary and subsequently dying from cerebrovascular lesions of various types.

Methods and material.—In the course of the investigation we have examined 48 patients and in the majority a radiopaque substance was injected at the time of necropsy. Cannulæ were placed in both the carotid and the vertebral arteries, the external carotid artery was ligated and the brain then injected with a solution of silver iodide in 15 per cent gelatin; a procedure which facilitated subsequent dissection and allowed of radiological study. Initially the artery was removed from the vertebral canal at the time of the necropsy, a procedure we later abandoned in favour of removing the spine intact from the atlas to the seventh cervical vertebra with the carotid and vertebral arteries in situ. After fixation the carotid arteries were examined throughout their length; the spinal cord was removed from the spine and the spine, stripped of muscles, was placed in 6 per cent nitric acid. The resulting decalcification of the vertebræ enabled us to dissect the specimen more easily and to carry out a detailed examination of the artery within the vertebral canal.

FIG. 1.—Drawing of a dissection of normal vertebral artery within the vertebral canal.

Anatomy.—Before presenting our results we would briefly recapitulate certain anatomical features of the vertebral artery which we found to have significance in this study. The variation in size of the vertebral arteries so commonly encountered in the intradural portion of the artery is maintained throughout its length. The variations we found were of the same order as those described by Stopford (1916) who, in 150 specimens, found the left to be the larger in 51 per cent, the right the larger in 41 per cent and the arteries of equal size in only 8 per cent. We would stress the intimate relationship the artery bears on its medial aspect to the neurocentral joint (fig. 1) within the vertebral canal, and the fact that it is at this point that the artery passes immediately anterior to the emerging cervical nerve root, each root being supplied by a small arterial twig.

This anatomical relationship assumes importance when the cervical vertebræ are affected by degenerative osteo-arthritic change; this condition was present in several of the specimens we examined. That the neurocentral joint is frequently affected in cervical spondylosis was emphasized by Pallis, Jones and Spillane (1954) in their most recent study of the condition. The bony prominence which develops displaces the artery laterally and in the more severe cases in an anterior direction also. The displacement so produced varies from a gentle curve (the left vertebral in fig. 2) to a marked distortion (figs. 2 and 3).

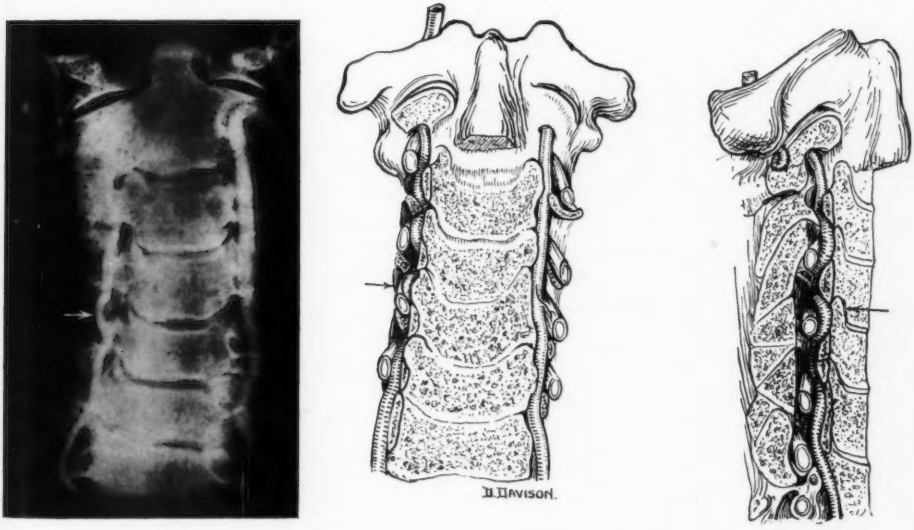

FIG. 2.—A radiograph and drawings of a specimen to show the distortion of the vertebral artery by osteo-arthritis of the "neurocentral joint." Arrows indicate comparable points on the severely distorted side.

Results

We may say at the outset that we have found atheroma to be a common lesion of the vertebral artery in the neck. The stenosis so produced plays, we believe, an important part in the pathological background of certain of the clinical syndromes associated with occlusion of the internal carotid artery. It also plays an integral role in the production of a cerebellar infarction of a distinctive type.

We have, therefore, considered our results under the following three headings:

(1) Incidence of atheroma in the vertebral artery in the neck.
(2) Atheroma of the vertebral artery in relation to disease of the carotid artery.
(3) Concomitant cerebral and cerebellar infarction.

(1) *Incidence of Atheroma of the Vertebral Artery in the Neck*

In this series of 48 patients, dying as a result of various cerebrovascular lesions, a significant degree of atheroma of the vertebral artery was encountered in 19 patients. The degree of atheroma has varied from a localized plaque with little or no stenosis to diffuse involvement of the artery. On three occasions the artery was occluded and in each instance a superadded thrombosis was responsible for the final occlusion. In a further ten instances the plaque had reduced the lumen of the artery by more than half the cross sectional area. Our series is not sufficient in number for us to speak with certainty of a "typical site," for the atheroma was found in all parts of the artery; nevertheless there does appear to be a definite tendency to contiguous involvement of the vertebral when the subclavian is affected by atheroma (fig. 7). In such cases there is usually appreciable narrowing of the mouth of the artery and for the first inch or so of the vessel. We found no increased tendency to atheroma in the artery in its tortuous course around the axis and atlas, nor did we find it occurring with any marked frequency on the curvatures of the artery which, as we have shown, develop in association with cervical spondylosis. Similarly variation in degree of atheroma was not related particularly to the size of the vessel, sometimes the larger sometimes the smaller being the more involved.

Histological examination of the artery was carried out in all cases where the artery was macroscopically abnormal; with the single exception of one example of cystic medial necrosis, only the typical appearances of atheroma were seen. On two occasions hæmorrhages were seen in the base of plaques similar to those described in the carotid artery (Yates, 1954). Such intramural hæmatomata are a common finding in atheromatous carotid arteries and may be seen in all stages of organization and absorption. Changes resembling those of thrombo-angiitis obliterans were not observed.

It was not possible to infer the presence of atheroma in the vertebral

artery from the appearances of the vessels elsewhere in the brain. As a broad generalization, if the intracerebral vessels and carotid arteries were involved by atheroma, then the chances of the vertebral artery being similarly affected were high. But healthy intracerebral vessels do not imply healthy vertebrals, and we have come to realize that examination of the vertebral artery throughout its length is essential to complete the pathological examination in cases of cerebrovascular disease.

(2) *Atheroma of the Vertebral Artery in Relation to Disease of the Carotid Artery*

The importance of the vertebral arteries as collateral channels is seen primarily in cases where the carotid circulation on one or other side has been occluded either in surgical treatment or by disease. Because of this we have paid particular attention in this series to the vertebral arteries where disease of the carotid artery was known to be present.

A "significant" degree of atheroma of the carotid artery was seen in 15 necropsies and we have taken as an arbitrary standard for significant a reduction of the lumen of the artery by one-half or more at its narrowest point. In 9 of these patients atheroma was present in the vertebral arteries, only in 6 were the arteries completely free of disease. The resultant stenosis varied from moderate narrowing in 2, to severe narrowing in 5; in 2 others final occlusion occurred in a stenosed vessel through an additional thrombosis. In 4 of the cases the atheroma was confined to one vertebral artery.

In the 15 cases of atheroma of the internal carotid artery the occlusion of the carotid was complete, or nearly so, in 3 cases. The first patient presented with a single episode of sudden hemiplegia, the clinical picture being typical of a vascular occlusion. At necropsy it was seen that the occlusion of the right internal carotid artery had only given rise to cerebral infarction when the thrombus finally extended into the middle cerebral artery on the same side. Until this occlusion occurred the collateral channels through the remaining carotid and the vertebral arteries, being both patent and healthy, had maintained an adequate blood supply.

The second patient showed in addition to an infarction of a hemisphere an infarction of the cerebellum of a distribution which is associated, we believe, with failure of the vertebral collateral circulation. The clinical details will be recorded in full in the next section.

The third patient with carotid artery occlusion is here reported in detail since not only was the history a typical one of recurring episodes of motor and sensory disturbance, but we believe that it shows clearly the part the vertebral artery plays in the syndrome of carotid artery occlusion.

R. G. (male, aged 60). Admitted under the care of Dr. Fergus R. Ferguson on 6.6.55. In 1951 the patient developed both intermittent claudication and

angina of effort. These did not greatly incapacitate him until one day in September, 1953, without premonitary symptoms, the left arm suddenly became numb and weak. The symptoms persisted for one day only and then recovered without any residual disability. For the next eighteen months frequent attacks of numbness occurred, sometimes affecting the left arm sometimes the right, and never lasting more than a few minutes. In March, 1955, the first of many attacks of unconsciousness occurred. Of sudden onset, the attacks only lasted for one or two minutes and it was on account of these that he was admitted to another hospital for investigation. On 27.4.55, whilst still an in-patient, he suddenly became unconscious, and on regaining consciousness some hours later a dense left hemiplegia with hemisensory loss was noted and these persisted until his death. The cerebrospinal fluid examined nine days later gave the following result: "A slightly xanthrochromic fluid. Cells 7 c.mm. Protein 126 mg. per cent. Globulin—slight excess. The Wasserman and Kahn reactions were negative." Because of the high protein in the cerebrospinal fluid and the persisting signs the possibility of cerebral tumour was considered and he was referred to Mr. R. T. Johnson.

Examination on 6.6.55 had revealed the following: Blood pressure 150/110. Heart normal. Carotid pulsation detected on both sides but pulsation on the right was perceptibly less than on the left. Central nervous system: Comprehension slow and co-operation poor. No dysphasia but tendency to perseveration in speech. On confrontation testing of visual fields there was a dense left homonymous hemianopia. A left facial weakness was combined with a profound paresis of the left arm and weakness of the left leg. The reflexes of the left limbs were brisker than the right and the left plantar response was extensor. Sensation, as far as could be assessed, showed impairment of all modalities on the left side of the body.

Later in the day a generalized convulsion occurred and the patient went into coma. The diagnosis of thrombosis of the right carotid was substantiated by angiography. There was no recovery from the coma and death occurred four days later.

Post-mortem examination.—A well nourished elderly man. The left ventricle was slightly hypertrophied, the total heart weight being 380 grammes. Both lungs were congested and œdematous. All other organs, apart from the brain, were essentially normal. The major arteries throughout the body showed a moderately severe degree of atheroma.

Brain (fig. 4): There was some enlargement of the right cerebral hemisphere with flattening of the gyri of the right parietal lobe. In this region the vessels of the pia arachnoid were dilated and there were a few petechial hæmorrhages. There was no gyral atrophy nor any superficial evidence of old infarction. On sectioning the brain an old softening was observed in the right insula region and neighbouring white matter which was of about two months' duration. A recent infarction of the cortex and white matter of the right parietal lobe was of approximately two to four days' duration and an infarction of similar age involved the left globus pallidus and adjacent part of the left internal capsule.

The cerebellum and brain-stem were normal.

Vessels: The left internal carotid artery was almost completely occluded at the sinus by atheroma with many deposits of calcium in the occluding plaques (fig. 4). The right carotid artery showed a recent thrombosis (fig. 4) and the clot had extended upwards into the right middle cerebral artery. Apart from a moderate degree of atheroma of the basilar and vertebral arteries within the skull, the other components of the Circle of Willis and the intracerebral vessels were normal in appearance. The vertebral arteries in the neck showed extensive

atheroma. On the left side the vessel was narrowed by plaque 3 cm. long opposite the fourth and fifth cervical vertebræ; the artery on the right side was stenosed to a similar degree at the level of the fifth cervical vertebra and again as it passed through the axis (fig. 4).

Comment

In spite of clear evidence, both clinical and pathological, of atheroma in the major vessels elsewhere, the intracerebral vessels were remarkably healthy apart from some atheroma in the basilar and vertebrals within the skull. We were at pains to confirm this finding by dissection of each individual artery. Also a careful search of the brain itself did not reveal any lesion of sufficient age to account for the recurring attacks of sensory and motor disturbances in the limbs. Furthermore, judging from the histological appearances, only the left internal carotid artery was occluded at a time when episodic sensory disturbances were occurring in both right and left limbs with equal frequency, the occlusion of the right carotid artery being a terminal event.

Symonds (1955) describes a very similar patient and suggested "that this episodic loss of function, which must be ischæmic, is not due to any fresh vascular obstruction but to a temporary failure of the compensatory mechanisms." We feel that this interpretation is the only reasonable one in the patient we have described, the widespread atheroma of the vertebral arteries in the neck playing an important role in the production of symptoms. It is significant that symptoms appeared to arise in the post-central area, the junctional territory between the carotid and vertebral circulations. If such an interpretation be admitted then it is necessary to offer some explanation for the episodes of transitory cerebral circulatory failure. Changes in regional blood flow, local CO_2 concentration, or alterations in blood pressure may be operative in some cases but they do not offer an altogether satisfying explanation of the observed clinical facts. We would draw attention again to the small intramural hæmatomata observed in both the carotid and vertebral arteries in this and many other cases. It is a frequent experience in carotid angiography that trauma to the arterial wall during the injection of dye may cause transient spasm of the carotid artery. We suggest that intramural hæmorrhages, by suddenly distending a segment of the arterial wall, operate in a similar way and the spasm so produced may lead to a temporary imbalance of the cerebral circulation. This mechanism could well account for the transient clinical phenomena so commonly seen.

These considerations have more than a theoretical value. Recently Eastcott, Pickering and Rob (1954) described relief of transitory sensory episodes following reconstruction of the diseased carotid artery with an arterial graft. Certainly if one regards the episodes as indicative of impending failure of the collateral channels, then reconstruction of the carotid artery in these cases seems to us to be the most rational line of treatment.

(3) *Concomitant Cerebral and Cerebellar Infarction*

In this series we have encountered 4 patients where an infarction of a cerebral hemisphere was accompanied by infarction of the cerebellum, which in 3 was bilateral. Knowledge of the state of the vertebral arteries in the neck has provided a reasonable pathological interpretation of the sequence of events. The fact that these patients were seen over a relatively short period suggests that such lesions may well occur more frequently than has been recognized previously. In view of their intrinsic interest we are reporting these patients in detail.

J. P. (male, aged 77). Admitted 2.4.55. Apart from an operation four years previously for the repair of a hernia the patient had been in good health. Two weeks previous to admission he had a "heart attack" consisting of sudden loss of consciousness with cyanosis. A similar attack occurred two days before admission. Over the next forty-eight hours seven further attacks occurred, each being accompanied by loss of consciousness for times varying from one to five minutes.

On examination the abnormalities were confined to the cardiovascular system. The pulse rate between attacks was thirty-four per minute, the attacks being accompanied by asystole for varying periods. The blood pressure was 145/55 and œdema was present over the ankles and sacrum.

Complete heart-block persisted and on the night of admission repeated attacks caused loss of consciousness for an hour. The attacks continued and the patient died in coma twenty-four hours later.

Post-mortem.—The heart weighed 450 grammes, the increase was due to left ventricular hypertrophy. An extensive infarction of the anterior wall and adjacent interventricular septum appeared to be about two weeks old. The coronary vessels were severely atheromatous, in particular the anterior descending branch was almost completely occluded at its origin. All the major arteries examined showed similar extensive arteriosclerotic changes. The lungs were œdematous. A large active chronic ulcer occupied the posterior wall of the first part of the duodenum. All other organs of the body were essentially normal.

Brain (fig. 5): There was a very recent infarction of the right internal capsule and adjacent basal ganglia. No older infarction or scarring was present. There were some scattered areas of gyral atrophy. Older infarcts were present in both cerebellar hemispheres. Both were restricted to the cortex in the middle of the lobes; on the right side predominantly in the territory of the posterior inferior cerebellar artery, on the left side at the junction of the territories of the superior and posterior inferior cerebellar artery. The swelling of both infarcted areas had produced upward displacement with tentorial grooving. The brain-stem was normal.

Vessels: Apart from a few small plaques of atheroma in the walls of both posterior cerebral arteries, the Circle of Willis showed neither occlusion nor any significant degree of stenosis. The vessels of the cerebellum were normal and the intradural portion of the vertebral arteries showed a moderate degree of atheroma.

Vessels in the neck: On the left side, as the vertebral artery passed round the atlas, marked narrowing of the lumen was seen due to an atheromatous plaque. Superadded recent thrombosis completely occluded the vessel (fig. 5). The clot was about 1 cm. in length. The right side was also markedly narrowed in two places and atheromatous changes were present throughout its length.

Both the carotid arteries showed atheroma at the sinus. The lumen of the

right carotid was narrowed by 50 per cent with a hæmorrhage into the base of a plaque (fig. 5). The left was even more severely narrowed (fig. 5).

S. W. (female, aged 56). Admitted 21.2.55. The patient was admitted in coma with a history that she had been found in this state in a gas-filled room. Consciousness was regained an hour after admission when marked dysphasia and right facial weakness were noted. The blood pressure was 150/95. These findings and a failure to detect carboxyhæmoglobin in the blood led to the conclusion that the loss of consciousness at the onset was due to a cerebral thrombosis rather than carbon monoxide poisoning. Mental confusion was the most marked feature the following day. No further signs developed for forty-eight hours when she again lapsed into unconsciousness this time with a dense right hemiplegia. She remained unconscious until death occurred forty-eight hours later.

Post-mortem.—The spleen and left kidney both contained infarcted tissue of a similar age (about one week) the result of arterial occlusion by thrombus. No source of emboli was found in the heart which was normal. None of the other organs of the body showed any significant pathological change.

Brain: The left cerebral hemisphere was swollen with flattening of the gyri and herniation of the brain to the right beneath the falx and down through the tentorial opening producing a small cingulate and hippocampal herniation. On dividing the brain, the left hemisphere with the exception of the territory of the anterior cerebral artery was softened and œdematous. The appearances were those of an infarction of two to five days' duration. The left middle cerebral artery was thrombosed, though not severely atheromatous.

There were bilateral and approximately symmetrical areas of infarction in both cerebellar hemispheres (fig. 6). The areas involved lay in the middle of the lobes on the superior surface of the cortex in the territory of the superior cerebellar artery. The injected material in the vessels could be seen to enter the infarcted areas.

Intracerebral vessels: The intracerebral vessels, apart from the left middle cerebral artery, the vertebral artery within the skull and the basilar arteries, showed a little atheroma only. None of these vessels, nor any of the cerebellar arteries, were occluded or significantly stenosed.

Vessels in the neck: The right vertebral artery which was four times the diameter of the left was almost completely occluded by atheroma extending for 2 cm. from its origin from the subclavian. Throughout the rest of its cervical course the artery was free from disease. The small left artery was normal.

The left internal carotid artery was occluded at its origin, the right was normal

E. C. (female, aged 55). Admitted 26.8.55. The patient was under the care of Dr. A. Morgan Jones. She had been known to suffer from mitral stenosis for twenty years. During the past five years her dyspnœa had increased in severity until she could only walk a few yards without halting. Examination revealed a moderately enlarged heart, mitral stenosis and auricular fibrillation at a rate of 70. After consultation with Mr. Frank Nicholson it was decided that, in spite of her age and the presence of auricular fibrillation, mitral valvotomy offered the only chance of relief from an intolerable handicap.

The operation was carried out on 31.8.55 by Mr. Frank Nicholson, clot being removed from the left auricle and the mitral valve dilated. Although the operation was uneventful, recovery from the anæsthetic was delayed. It was realized then on examination that a right hemiplegia had developed. Immediately after this, signs of an occlusion of the left iliac artery were noted and in an effort to save the limb an embolectomy was performed. The patient never regained consciousness and died the following day.

Post-mortem.—The heart weighed 350 grammes and showed left auricular and

right ventricular hypertrophy. There was a recent operative wound in the left auricular appendage which contained newly formed thrombus. The mitral valve, thickened and fibrous, had been successfully split to admit one finger. The left common iliac artery contained a little mural thrombus near the site of the embolectomy wound. Apart from collapse of the right middle lobe the lungs were normal. Other organs of the body showed no significant pathological changes.

Brain: A little swelling of the left cerebral hemisphere had caused a small cingulate herniation beneath the falx. The upper half of the pre- and post-central gyri were mottled with petechial hæmorrhages and the cortex here was swollen. The central white matter beneath this region showed early softening.

A region 2 cm. in diameter in the middle of the left cerebellar hemisphere in the territory of the superior cerebellar artery was hæmorrhagic and softened. The rest of the brain, in particular the brain-stem, was normal. None of the intracranial arteries were diseased and none were occluded or stenosed.

Vessels in the neck: Both carotids showed extensive atheroma extending from the common carotid arteries for 3 cm. above the sinuses[1] of the internal branches. Both were markedly narrowed. The vertebral arteries showed similar changes

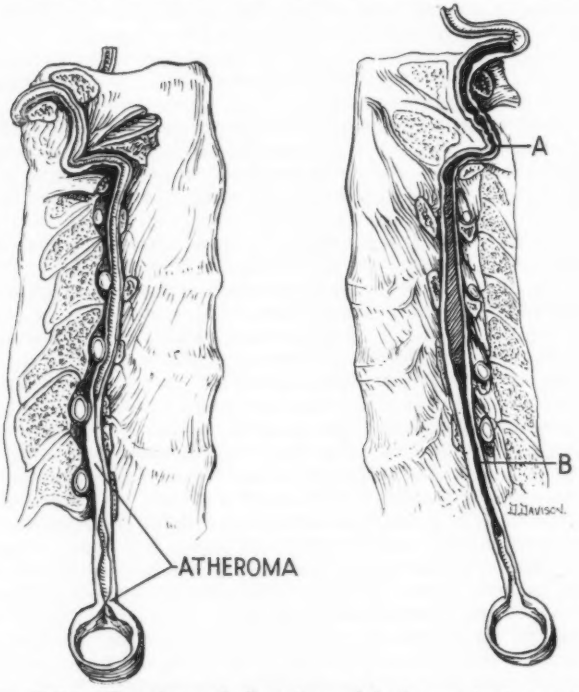

FIG. 7 (Case E.C.).—Drawings of dissection of both vertebral arteries. On the right there is extreme narrowing by atheroma extending up from the subclavian artery. The left vertebral, also atheromatous, is thrombosed at two levels (A and B).

[1]The term "sinus" in this article refers to the sinus at the origin of the internal carotid artery.

(fig. 7). The right was narrowed to a slit in the first 5 cm., the left was occluded in two places by thrombosis superimposed on extensive atheroma.

L. A. (female, aged 73). Admitted 21.1.55. Apart from intermittent pains in the hips due to osteo-arthritis, the patient had been in good health until four days prior to admission. Without premonitory symptoms she suddenly developed unsteadiness of all four limbs and her gait became markedly ataxic. From the onset she complained of headache over the right eye. She went to bed and within two hours of the commencement her speech became slurred and indistinct but there was no associated dysphagia. On the fourth day of the illness she was admitted to hospital.

Examination: Very obese elderly female with signs of generalized osteo-arthritis. Blood pressure 250/140. Central nervous system: Mental state was dull and apathetic and co-operation was poor. Marked slurring dysarthria. Fundi showed scattered perivascular hæmorrhages and exudates but no papillœdema. There was no impairment of power, but formal testing revealed signs of ataxia of both arms and legs. Reflexes equal in all four limbs. Right plantar response extensor, left gave an indefinite response.

The following morning there was a gradually increasing impairment of consciousness and by evening she was comatose. She remained in this state for a further three days when she died.

Post-mortem.—There was very considerable left ventricular hypertrophy, the total heart weight being 600 grammes. Apart from pulmonary congestion other organs of the body showed no significant pathological changes. The aorta and major arteries were severely atheromatous.

Brain: The left cerebral hemisphere was swollen and slightly flattened in the region of the superior parietal lobule, and the cortex and underlying white matter were infarcted and hæmorrhagic. There was an old cystic area in the right lenticulocaudate region. Both cerebellar hemispheres showed symmetrical areas of hæmorrhagic infarction, each about 2 cm. diameter. The infarctions lay on the posterior border of the cerebellum in the area between the territories supplied by the superior and posterior inferior cerebellar arteries.

None of the intracranial vessels showed more than minor atheromatous changes, none were stenosed or occluded. The cerebral veins and venous sinuses were normal.

Vessels in the neck: The common and internal carotid arteries contained many plaques which, in the sinuses, had caused considerable stenosis. The vertebral arteries were also narrowed at many points, the right one (the larger) being reduced to about a quarter of the normal lumen at the level of the axis.

Discussion

The demonstration of an occlusion of the cervical portion of the carotid artery at necropsy has provided an explanation for many cases of cerebral infarction which, in the past, had often been attributed to local vasospasm. The 4 cases that we have described illustrate clearly that atheroma of the vertebral artery within the vertebral canal may act in a similar fashion in producing infarction of the cerebellum. The infarcts which result from a critical reduction of blood flow through the vertebral artery in the neck are very different in distribution to those infarctions which follow occlusion of the individual cerebellar arteries. In the first place, the brain-stem in our cases showed no evidence of infarction although the function of the vital centres in the brain-stem may well have been impaired in the

terminal stages. In the second place, in 3 of our cases the infarcts were bilateral, approximately symmetrical, and in relation to the territory of the superior cerebellar artery. If the vertebral circulation should fail then the effects of ischæmia would be most marked in the area supplied by the terminal branches of the basilar to the hind-brain. We have been surprised at the frequency of these lesions and it is certain that they occur more commonly than is generally recognized since these 4 cases were seen in an unselected series over a relatively short period of time.

The clinical picture in these 4 patients was remarkable in only one, where the sudden onset of signs of a bilateral cerebellar lesion occurred four days before death. In the other 3 patients the effects of cerebral hemisphere infarction obscured all other signs. The failure of the cerebral circulation was precipitated in two patients by extraneous circumstances. In one (case J. P.) heart-block with periods of asystole was responsible, in the other (case E. C.) a surgical operation was the indirect cause. In neither patient was there any historical evidence to suggest that there was pre-existing disease of the major cerebral vessels. Unfortunately, we did not have the opportunity of examining these patients before their terminal illness, and we were not able to repeat the interesting observations made by Biemond (1951). He found in a series of patients with cerebral arteriosclerosis that rotation and extension of the head produced nystagmus, slight dysarthria and a transient abnormality of the plantar response.

Biemond, in discussing the mechanism of production of these signs referred to de Kleyn's (1939) work on postural vertigo. de Kleyn, in a series of cadavers, found that rotation and extension of the head to one side obstructed the contralateral vertebral artery. The condition of the arteries in the neck and of the spine were not described in detail and we feel that atheroma, producing stenosis of the vertebral artery, may well play a part in the production of such signs in cases of cerebrovascular disease. The possibility also arises that cervical spondylosis, common enough in this age group and capable of distorting the vertebral artery, may play a subsidiary role in obstructing one or other vertebral artery during movement of the cervical spine.

Summary

(1) 48 patients were examined and atheroma of the vertebral artery in its cervical portion was noted in 19 patients.

(2) Frequently found in association with atheroma of the carotid artery at the sinus, it is suggested that the resulting stenosis of the natural collateral channels plays an important part in the development of certain symptoms associated with occlusion of the internal carotid arteries.

(3) Attention is drawn to the distortion of the artery caused by bony changes in the spine in cervical spondylosis.

(4) 4 cases of cerebellar infarction are described. In all cases the verte-

PLATE XX

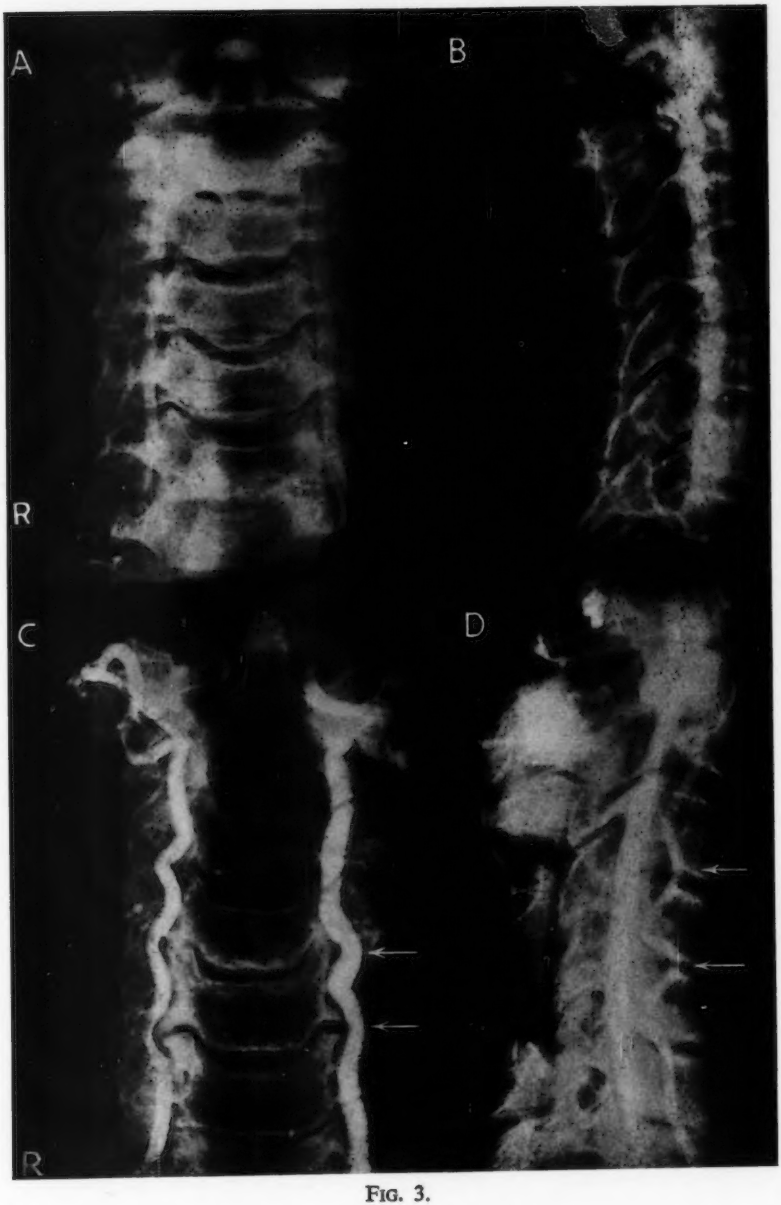

FIG. 3.

To illustrate article by E. C. Hutchinson and P. O. Yates.

PLATE XXI

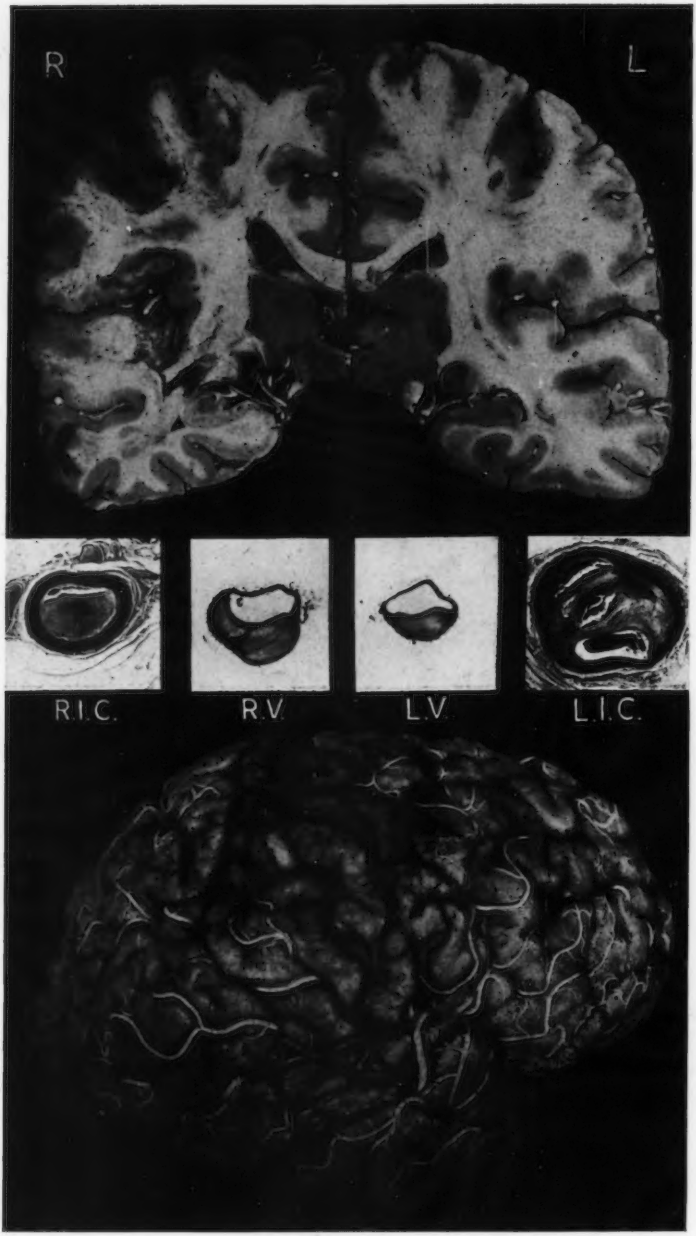

FIG. 4.

To illustrate article by E. C. Hutchinson and P. O. Yates.

PLATE XXII

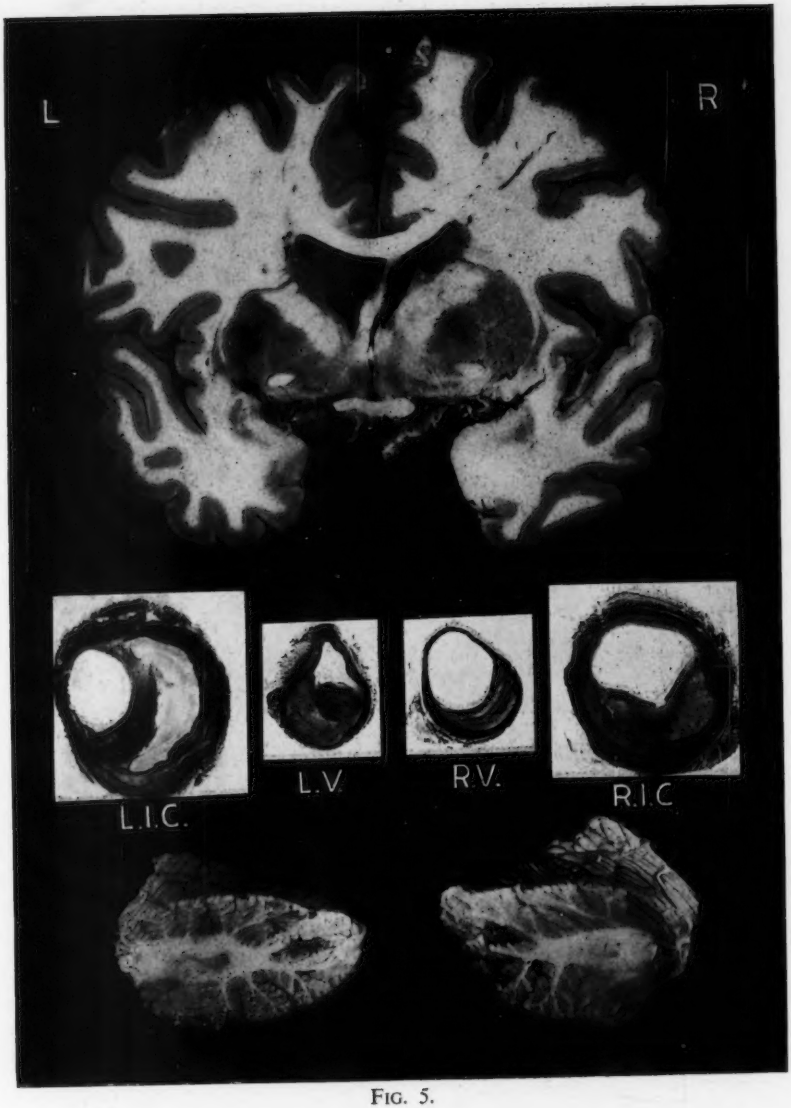

FIG. 5.

To illustrate article by E. C. Hutchinson and P. O. Yates.

PLATE XXIII

FIG. 6.

To illustrate article by E. C. Hutchinson and P. O. Yates.

bral and carotid arteries were stenosed by atheroma, and in each case an infarct of one or other cerebral hemisphere was present.

ACKNOWLEDGMENTS

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LEGENDS FOR PLATES

PLATE XX

FIG. 3.—Radiographs of specimens—vessels injected with silver iodide in gelatin. A and B—Normal appearance of vertebral artery. C and D—Arrows indicate lateral and anterior displacement of the artery by osteo-arthritis in the region of the "neurocentral joint."

PLATE XXI

FIG. 4 (Case R.G.).—The photograph of the right hemisphere showing the fronto-parietal region where vessels failed to inject though no occlusion could be found. Almost all the filling has presumably taken place via the vertebral arteries. The brain section shows the recent infarction of the right fronto-parietal regions. An old (about two months) cystic infarct replaces part of the right insular cortex. The left internal carotid artery is almost occluded by atheroma—the two upper spaces being hæmorrhages into the plaque. The right internal carotid artery whilst showing some atheroma at the sinus was completely occluded by a recent thrombosis. The section is from a point 1 cm. below the base of the skull, and shows thrombosis only. Both vertebral arteries are severely atheromatous, these sections being from the levels of the fifth cervical vertebra.

PLATE XXII

FIG. 5 (Case J.P.).—The right corpus striatum is swollen and blurred by a recent infarction. The left internal carotid artery (LIC) and the right internal carotid (RIC) are severely narrowed by atheroma. The left vertebral (LV) is shown narrowed by thrombus adherent to a plaque of atheroma; it was completely occluded, the rest of the thrombus having been accidentally dislodged. Both cerebellar hemispheres show softened areas of the same age, that on the left being in the territory of the superior cerebellar artery, that on the right at the extremity of the circulation of the posterior inferior cerebellar artery.

PLATE XXIII

FIG. 6 (Case S.W.).—Two recent hæmorrhagic infarcts both in the territory of the superior cerebellar artery. The injected arterial branches can be seen running into the infarct.

SPINAL CORD INVOLVEMENT IN MULTIPLE MYELOMATOSIS

BY

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MYELOMAS of the spinal column occur frequently in multiple myelomatosis and Batts (1939) found radiological evidence of them in 70 per cent of cases. Unlike cranial myelomas, however, encroachment upon nervous tissue often results, and next to root pain, spinal compression is the commonest neurological complication of the disease (Adams, Alling and Lawrence, 1949). In addition, lesions other than those due to compression are said to affect the cord. It is proposed to consider here both types of spinal cord involvement.

SPINAL COMPRESSION

Material.—The present series comprises 20 cases (Table I) in each of which the spinal lesion had been verified histologically either at operation or at autopsy.[1] One additional case of myelomatosis with clinical evidence of cord compression but in which an autopsy could not be carried out, will also be mentioned. All but this case had been seen in neurological or neurosurgical departments.

Literature.—In a review of the literature a total of 204 cases of multiple myelomatosis with spinal compression were discovered. Only 157, however, were described in adequate detail.

Incidence.—The incidence of this complication may be greater than some authors suggest. Thus if it occurs in the terminal stages of myelomatosis and is of mild degree it may be overshadowed by other features and neglected, as probably took place in the cases of Permin (1907, Case 3), Glynn (1914, Case 2) and Dalgaard and Dalgaard (1952, Case 2). Figures given by different authors vary considerably, the range being from 45 per cent (Kirshbaum, 1947) to 5 per cent (Magnus-Levy, 1932: Sarasin, 1950) but Fowler and Gordon (1950)—11·5 per cent, Langley and Scott (1954)—15 per cent, Batts (1939)—18 per cent and Evans and Johnston (1949)—20 per cent were dealing with small numbers of cases. On the whole it seems that about 6 per cent of patients with myelomatosis develop sufficient spinal compression to produce a disability that warrants

[1] Sixteen cases have been included in a Thesis for the degree of M.D. in the University of Durham (1954), entitled "Neurological Aspects of Multiple Myelomatosis."

active treatment and Svien, Price and Bayrd (1953) have given an identical figure. The incidence of spinal compression of all degrees is, however, probably about 20 per cent.

The frequency of spinal myelomas with cord compression amongst spinal cord neoplasms is also difficult to determine and is dependent upon the author's type of practice. Thus Elsberg (1941, p. 428) found that they comprised 6 per cent and Grosz (1925) 4·8 per cent of extra-dural tumours, whereas Shenkin, Horn and Grant (1945) gave an equivalent figure of 35 per cent. Stratemeyer (1950) states that of 121 cases of paraplegia at autopsy, 40 per cent were due to epidural metastatic tumours, 5 per cent of which were myelomas.

Pathology.—Compression of the spinal cord or cauda equina by a myeloma may be produced by either (1) extension of the tumour from the vertebra, with or without bony collapse or (2) a primary epidural myeloma.

(1) *Vertebral myeloma:* This is by far the most common finding for they were present in all but a few of the cases in the literature. They were either single or multiple and in 60 per cent of cases the former type occurred. It is unlikely, however, that this figure is accurate because neither full radiological nor pathological examinations of the spine were always carried out. Mazet (1951) and Young and Funk (1953) have indicated the value of more careful study in this regard. In the present study, 4 cases (Table I: Cases 5, 7, 10 and 18) had no bony lesion and of the remainder 15 had single vertebræ affected during the period of observation.

The site of the myeloma producing cord compression could be ascertained in 193 cases and 33 were in the cervical region, 134 in the thoracic and 26 in the lumbar. The precise level was given in 166 instances, and the higher incidence in the thoracic spine (fig. 1) is not dependent upon the larger number of bones it contains, as was the case in Frazier's (1918, Table XXI, p. 557) series of primary neoplasms. The fourth, fifth and sixth thoracic vertebræ were the most frequently involved and cord- or cauda-compressing myelomas at the extremities of the spine were relatively uncommon. The highest incidence was in the middle 5 thoracic vertebræ and the lower 9 were the site of about one-third of all the tumours (fig. 1). Geschickter and Copeland (1928) and Sproul (1941) also incriminated the lower thoracic region but Lichtenstein and Jaffe (1947) when considering spinal myelomas with and without spinal compression, found the lumbar spine to be the commonest site. This is perhaps borne out by the frequency of low back pain in myelomatosis. It seems possible that the higher incidence of compressing myelomas in the mid-thoracic spine is due to a relative paucity of blood supply to this part of the cord. This has been shown in decompression sickness (Haymaker, 1954) and the cord complications of spinal anæsthesia (Williams, 1954).

The body of the vertebra is the commonest site for a myeloma but, as with other bony tumours (Frazier, 1918, p. 553), the laminæ or spinous

TABLE I

20 CASES OF SPINAL MYELOMA WITH CORD COMPRESSION

Case No.	*Sex*	*Age*	MYELOMA		*Presenting symptom*	*Multiple or single*
			Level B = Bone C = Cord	*Part of vertebra*		
1	M	37	T 4 (B)	Body	Weak legs	M
2	M	37	T 4 (B)	Body	Back pain	M
3	M	67	T 8 (B)	Laminæ	Back pain	M
4	M	40	C 7 (B)	Laminæ	Neck pain	?
5	M	54	T 2 (C)	Bone normal	Back and root pain	M
6	M	49	L 3 (B)	Body	Buttock pain	? M
7	M	30	T 8 (C)	Bone normal	Back pain	M
8	F	53	T 5 (B)	Body	Shoulder pain	M
9	F	61	T 4 (B)	Body	Back pain	? S
10	F	62	T 2, 3, 4 (C)	Bone normal	Shoulder pain	S
11	M	32	T 8 (B)	Body and laminæ	Weak legs	?
12	F	53	T 1 (B)	Body	Weak and numb legs	M
13	F	48	T 2 to T 9 (B)	Bodies	Back pain	M
14	M	57	L 1 (B)	Body	Back pain	M
15	F	66	T 8 (B)	Body	Back pain	M
16	M	50	L 3 (B)	Body	Back pain	M
17	M	43	T 12 (B)	Body	Back pain	M
18	F	60	T 6, 7 (C)	Bone normal	Back pain	M
19	M	43	T 5 (B)	Laminæ	Back pain	M
20	M	74	T 7 (B)	Body	Back pain	M

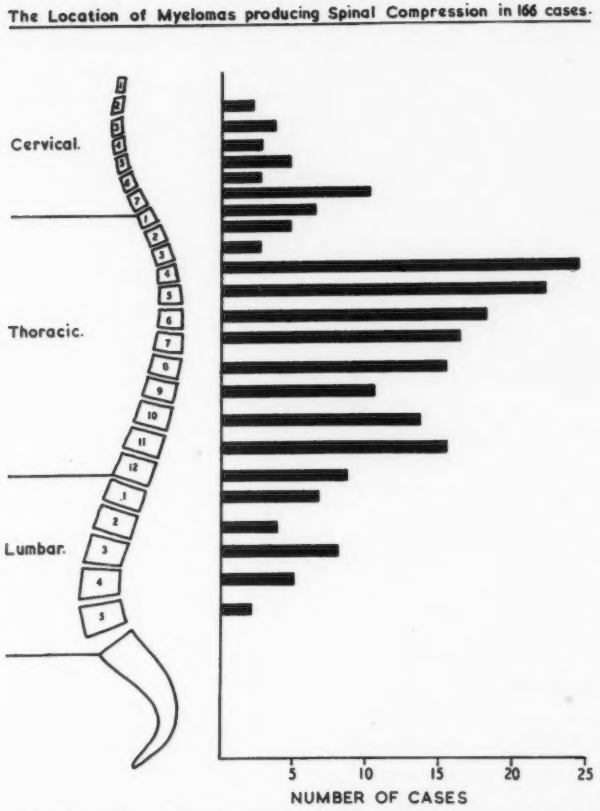

FIG. 1.—The location of myelomas producing spinal compression in 166 cases.

processes may be attacked primarily (Bell, 1933: Kamman, 1941: Snyder and Wilhelm, 1948: Christopherson and Miller, 1950: Cases 3, 4 and 19) (fig. 7) with extension of the tumour into the spinal canal. In Cases 6 and 14 laminal lesions were secondary to involvement of the vertebral body (fig. 4). As well as vertebral myelomas, those arising from a rib can grow into the spinal canal to damage nervous tissue (Thomas, 1901: Wells, 1921: Ford, 1952, Case Path. 12819u-8625).

The myelomatous tissue having replaced bone of the body or laminæ, in some cases extends into the spinal canal. There it surrounds the dural tube with a compressing collar which is usually thicker on the posterior aspect (fig. 2). Invasion of the dura mater very rarely occurs and in most cases the membrane erects an effective barrier to the advance of the myelomatous tissue (fig. 3). At operation, it is usually possible to strip

the tumour off the dura easily, but some anteriorly placed portions and extensions into the intervertebral foramina may be impossible to eradicate.

Myeloma tissue may also grow paravertebrally, either by direct extension from the body or other part of the vertebra, or by way of the foramina. It can collect anteriorly (Gaube, 1925: Kirschbaum, 1947: Case 5) or extend into the deep muscles of the back where it is found by the surgeon during his approach to the spine (Cases 1, 9, 14 and 19). In Case 14 (fig. 8) an extra-vertebral outcrop produced a subcutaneous tumour and in Case 18 a similar mass extending from the spinal canal at the level of T.3 to T.4 could be seen as a mediastinal shadow in radiographs of the chest. The paravertebral tumour is usually well differentiated from surrounding tissues and in one case (Case 14) the periphery was faintly calcified (not seen in fig. 8).

Compression collapse of the vertebral body, as in other neoplastic processes, is a sequel of the myelomatous invasion and as it occurs in almost half of all cases (Snapper, Turner and Moscovitz, 1953, p. 22) is the commonest pathological fracture in the disease. Collapse of varying degrees took place in Cases 6, 8, 9, 15, 16, 17 and 20 and it frequently progressed despite surgical and radiation therapy (fig. 7). In Case 15, the bony compression was so severe that it was difficult at autopsy to identify the affected vertebra; contrary to the usual findings, the intervertebral disc had disappeared. When a vertebral body collapses, myeloma tissue does not necessarily find its way into the spinal canal, for in Case 12 cord compression was due to bone alone. If a hæmorrhagic tendency exists, extra-dural bleeding may accompany the bony changes and accentuate spinal compression; this occurred in the patient of Beck (1942) and probably in that of Toušek and Vortel (1947).

Occasionally, instead of a local lesion in the spine there may be generalized osteoporosis (Lettow, 1952) and vertebral collapse readily results. This together with spinal compression took place in the case of Gilbert-Dreyfus, Mamou and Attal (1947) and also in the case excluded from the present series. In the latter, the bone changes were so severe that radiography was almost impossible.

(2) *Epidural myeloma:* In the present series there were 4 cases (Table I: Cases 5, 7, 10 and 18) with no apparent bony involvement and in its absence spinal compression may conceivably be due to a myeloma arising from one of several structures. (*a*) A characteristic of the myeloma is that it never originates from nervous tissue so that this source may at once be excluded; the "plasmoma" described by Verda (1944) was probably associated with dura rather than spinal root. (*b*) The spinal dura mater invariably resists the advance of myelomatous tissue (fig. 3) but occasionally, as in the cranium, microscopic invasion takes place (Warstat, 1913; Davison and Balser, 1937); it seems unlikely, however, that this would compress the cord. Other authors (Hammer, 1894: Winkler, 1900:

Kaess, 1915: Scott, Stanton and Oliver, 1933, Case 4) have described dural myelomas but they were probably associated with adjacent vertebral disease and the only acceptable example of a primary myeloma of the spinal dura is that of Stratemeyer (1950). As myelomas of the cranial dura often erode overlying bone, it is possible that the bony destruction seen in some cases of spinal myelomas may similarly be secondary to the dural lesion. Pathological information on this unlikely occurrence is not available. (*c*) Malignant tumours of various types may originate from the lymphoid tissue said to occur occasionally in the epidural space (Luce, 1923: Browder and de Veer, 1939: Shenkin *et al.*, 1945). Certain published cases of primary epidural myeloma cannot be accepted because of inadequate information (Browder and de Veer, 1939, Case 6: Klemme, 1933, Cases 1, 2, 3, and 4: Shenkin *et al.*, 1945). On the other hand, Case 10 of the present series seems to be an example of this lesion. The vertebræ were normal, the myeloma could be readily removed from the dura mater and the patient has now survived fifteen years with no evidence elsewhere of the disease. Case 7 may be another, although a myeloma growing from the laminæ could not be entirely excluded. Although the radiographs were normal (fig. 6), this does not necessarily exclude myelomatous infiltration of bone (Wallerstein, 1951: Heiser and Schwartzman, 1952). It is possible that Cases 5 and 18 were similar because osseous and dural involvement were absent. They both had paravertebral extensions of myelomatous tissue, and in each the disease soon became widespread. It thus appears that an epidural myeloma without vertebral disease is commoner than the literature suggests for it occurred in 4 of 20 cases (20 per cent). However, as these patients present with spinal compression of undetermined ætiology, they are more likely to be seen in neurological practice. True primary epidural myelomas (Case 10 and perhaps 7, fig. 6) are probably very rare, and the other possible cases (Cases 5 and 18) were precursors of multiple myelomatosis. (*d*) Extension of an extraspinal myeloma into the epidural space occurred on one occasion (Schütz, 1914), but the reverse is more common (Gaube, 1925: Pines and Pirogowa, 1928, Case 1: Kirshbaum, 1947: Cases 5 and 18, fig. 8). Rib myelomas growing into the canal have already been mentioned.

Solitary myeloma: As more precise diagnostic techniques are employed and longer follow-up is possible, this entity becomes rarer. Concerning myelomas with spinal compression, tumours at first thought to be solitary, usually prove to be forerunners of the generalized disease (Dalgaard and Dalgaard, 1952: Ritz and Meyer, 1952: Rogers, 1953) although prediction of the outcome on histological grounds is impossible. Of the acceptable solitary myelomas that have been described, there are only 2 with spinal compression (Walthard, 1924: Raven and Willis, 1949). About a quarter of the cases with spinal myelomas and compression in the literature are said to have had no other evidence of myelomatosis but it seems likely that

investigations and follow-up were inadequate. Of the present series (Table I) only Case 10 can be considered a solitary myeloma; the tumour was proven histologically and the patient is still alive fifteen years later. Christopherson and Miller (1950) are therefore probably correct in believing that such a lesion exists. When generalized spread of the disease takes place, there is no information to suggest that it does so locally in the first instance as Dalgaard and Dalgaard (1955) have described. The amount of evidence indicating that myelomatosis accompanies the spinal myeloma may vary in degree, and in Case 20, there was only Bence Jones proteinuria and in Case 18, abnormal serum proteins, at the time of diagnosis.

Primary amyloidosis associated with myelomatosis is a recognized event (Magnus-Levy 1933: Bayrd and Bennett, 1950) and amyloid tissue may occur in the substance of a vertebral myeloma. Cases with bony collapse and cord involvement have been described (Mandl, 1924: Freund, 1930: Gusmano and Strata, 1953: Pino, 1954) and others, including Case 11, where the material was present and probably contributing to the spinal compression have also been reported (Schütz, 1914: Klemperer, 1920: Kohlmann, 1921, Case 1: Bell, 1933, Case 89: McMahon, 1951).

Trauma was a factor in 16 per cent of all cases and usually related to the collapse of a diseased vertebra. Frequently the injury causing this was trivial and such episodes as carrying a weight on the head (Váradi, 1937, Case 3), pulling on the arm (Codounis, 1949, Case 4) and reaching (Carlson, 1936, Case 3) were sufficient. In Case 15 a vertebral body collapsed while the patient was being lifted in bed.

A myeloma may develop in previously damaged bone and in Case 14 (figs. 7 and 8) a traumatic crush fracture of the vertebral body became the site of a myeloma four years later; Flax (1941) described a similar happening. In Albert's (1951) second case, a true plasma cell myeloma grew in a vertebra that had previously been affected by chronic inflammation.

Spinal cord and root changes are due to direct pressure as produced by any compressing lesion and the damage may be local (Case 7) or extensive (Case 13—$T._2$ to $T._9$). The disease never enters the cord, and only Nicholls (1927) has described plasma cells in its substance.

Clinical Picture

Despite the various pathological changes encountered, the clinical findings are much the same.

The sex-incidence and age limits correspond with those expected for the disease as a whole. 90 per cent of the patients were in the fourth to seventh decades although the ages varied from 6 (Zäh, 1932) to 84 (Moeschlin, 1943, Case 4).

Presenting features: There are two distinct groups of patients: (1) those with spinal compression as the first indication of myelomatosis and (2) those in whom it occurred after the disease had manifested itself elsewhere.

(1) The first type of patient comprising 85 per cent, is seen by neurologists or neurosurgeons and the 20 cases comprising this report were of this kind. In some, no evidence of myelomatosis was forthcoming at the time of diagnosis, but investigations were occasionally inadequate. It was often impossible to estimate the period that signs of spinal compression antedated other features of myelomatosis, because the first appearance of Bence Jones proteinuria, serum protein abnormalities and small bony lesions cannot usually be determined. The interval, however, seemed to vary from six years (Jacox and Kahn, 1933, Case 1) to one month (Laesecke, 1927); in Case 16 it was five years and the initial lesion remained inactive. Back or limb pain is the commonest initial complaint and about three-quarters presented with it; of 20 cases (Table I), 17 had this feature. Its location in the back usually indicates the eventual site of spinal compression and thus interscapular pain is frequent. It is followed by cord symptomatology after an interval varying from three years (Rundles and Reeves, 1950, Case 21) to five (Case 12) or four (Case 2) weeks, during which time the pain increases in severity. 15 per cent of all cases presented with painless spinal compression, which did not differ from that produced by other pathological processes; Case 1, 11 and 12 are included here (Table I).

(2) The second group (15 per cent) contains those who develop cord symptomatology after the onset of the generalized disease. On an average it appears three to four months after myelomatosis has manifested itself elsewhere, and the fatal outcome is hastened.

The speed of onset of spinal compressions varies considerably. In Case 5, a complete paraplegia developed in two days, whereas in Case 18 of Cutler, Buschke and Cantril (1936), it took ten years to mature. A rapid onset is often associated with trauma or follows lumbar puncture but it does not necessarily indicate a bad prognosis as far as recovery of cord function is concerned.

Pain is the commonest symptom in myelomatosis and Snapper *et al.* (1953, p. 21) found it in 92 per cent of cases; in three-quarters it was back pain. However, only a small proportion of the latter develop spinal compression: 3 out of 12 (Evans and Johnston, 1949) or 1 out of 8 (Lawrence and Wasserman, 1950). Its characteristics are those of bone pain with root features, but apart from being more severe and persistent, it is not distinguishable from the pain of a spinal myeloma that does not lead to neurological complications. Despite the frequency of low back pain, lumbar myelomas compressing the cord are relatively rare (fig. 1). Occasionally the picture is complicated by pain originating from a prolapsed intervertebral disc, which was shown by myelography in Case 7 and probably also occurred in Case 16. Pain preceded the neurological features by weeks or months and as they appeared it became less; in only a few was it aggravated (Case 4).

Local spinal signs such as tenderness, deformity and rigidity are often

present and there was a local tumour due to extra-spinal extension of the myeloma in the cases of Davison and Balser (1937, Case 3), Mody (1943, Case 2) and in Case 14. If osteoporosis is severe, marked spinal deformities develop. This occurred in the case not included in the present series, and also in the case of Gilbert-Dreyfus, *et. al.* (1947).

Course and prognosis: The total survival period could be estimated in 145 patients and varied from four weeks (Zäh, 1932: Schluppli, 1939) to sixteen years (Wright, 1937: Campbell, 1951). Altogether, three-quarters of the patients were dead two years after the first symptoms whether they had been treated or not. One-quarter died within five months and only a fifth survived five years or more; Case 10, being a true solitary myeloma, is not considered here because the prognosis in this type of case should be excellent. Spinal compression combined with the established disease usually leads to a more precipitate downhill course. Cervical myelomas in particular produced a rapid demise (Zäh, 1932: Castleden, 1948). Details of death are known in 101 cases and in most of them it was directly attributable to the complications of spinal compression. The generalized disease was, however, responsible at times and in Case 16, the termination of the illness was heralded by widespread extension of it.

If treatment is inadequate, recurrence of the spinal myeloma is possible and a second decompressing operation was necessary in the cases of Ghormley and Pollock (1939, Case 6) and Svien *et al.* (1953, Case 7). In Case 11, the tumour was only partially removed and sixteen months later there was an extensive recurrence. Altogether there were 7 such patients, all of whom had made a good post-operative recovery initially.

Investigations

Radiographs of osseous myelomas reveal two main types (Paul and Pohle, 1940): one is cystic and trabeculated and the other, the one most frequently found in the vertebræ, is osteolytic and more destructive. The appearances may range from the erosion of one pedicle (Sparling, Adams and Parker, 1947, Case 18: Case 11) to complete destruction of the vertebra (Case 15). In some the laminæ may be chiefly affected (M.G.H. Case Records No. 26072, 1940: Case 4: Case 14—fig. 7) and in Case 5 the "soap-bubble" type of myeloma was found (fig. 4) extending from the body into a lamina; Hilton (1936, Case 1) had a similar example. After collapse of the vertebral body has taken place (fig. 5) complete destruction may ensue (Case 15) or if the process is arrested by treatment, sclerosis results (fig. 9). Although fractures in myelomatosis tend to heal well, possibly due to the high serum calcium (Snapper *et al.*, 1953, p. 24), spontaneous healing seems less likely to occur in the spine. If the myeloma extends beyond the vertebræ a paravertebral shadow may be seen on the radiographs (Cases 14 and 18) (fig. 8). In some cases, diffuse osteoporosis with severe and multiple vertebral collapse producing spinal compression may be found (Gilbert-

Dreyfus *et al.*, 1947: Lettow, 1952: Braun, 1955: Case excluded from present series).

In the presence of spinal compression, bony abnormalities may be occasionally absent, and although Wallerstein (1951) and Heiser and Schwartzman (1951) have shown that myelomatous infiltration of bones may still exist, it seems likely that the radiographs in Case 10, and in Case 5, 7 (fig. 6) and 18 also, were normal. The absence of radiological abnormalities of the spine, therefore, does not exclude the presence of a cord compressing myeloma.

The myelographic appearances in cases of spinal myeloma were in no way distinctive (figs. 6 and 8).

The cerebrospinal fluid had the features of the spinal compression syndrome. In only 2 cases was there a pleocytosis: Case 1 of Davison and Balser (1937) with 40 cells and Case 1 of Petrides (1939) with 16. Busser and Bugaut (1937) reported an occasional mononuclear cell but plasma cells have never been identified. The Lange curve abnormality present in 8 cases was probably due to the increased protein content of the fluid rather than the first-zone type of change that may occur with myelomatosis. In 4 cases, including Case 18, lumbar puncture was followed by a rapid increase of cord compression and surgery became an urgent necessity.

Differential Diagnosis

Before there is evidence of the generalized disease, the clinical diagnosis of a spinal myeloma with cord compression may be difficult or impossible. Thus, of the 7 cases reported by Svien *et al.* (1953) none had been diagnosed correctly before operation and in the present series, a correct pre-operative diagnosis was unusual. If there are no radiological bony changes present the nature of the lesion can only be determined at operation by microscopic examination (Cases 5, 7, 10 and 18).

In the presence of vertebral destruction and a paravertebral shadow, confusion with tuberculosis of the spine is possible (Cosacesco, 1948: Walch, 1949) and occurred in at least 13 cases in the literature as well as in the earlier considerations of Case 15. Metastatic carcinoma (Warstat, 1913) is common in the same age group and other vertebral tumours must be considered.

Treatment

Evaluation of treatment in multiple myelomatosis is difficult because there is a wide variety of possible clinical courses in the untreated patient.

Each of the 20 patients comprising this report had presented with features of spinal compression and in the 18 that were treated, therapy was directed in the first instance to the spinal lesion. 5 had operation alone, 12 had radiation therapy in addition to operation and one had irradiation supplemented by a cytotoxic drug (Table II). In the literature, 97 had

TABLE II

RESULTS OF TREATMENT IN 20 PATIENTS WITH SPINAL MYELOMA PRODUCING CORD COMPRESSION

Case No.	*Pre-therapy period*	*Therapy*	*Survival after therapy*	*Total survival*	*Present state*
1	3½ months	OP DXR	3 years +	3¼ years +	Fate unknown
2	—	None	—	6 months	Dead
3	—	None	—	3½ months	Dead
4	10 months	OP	2 months +	1 year +	Fate unknown
5	6 months	OP	5 weeks	7 months	Dead
6	4 months	OP DXR	3 years +	3⅓ years +	Working
7	12 months	OP DXR	4 years +	5 years +	Working
8	12 months	OP DXR	3 years	4 years	Dead
9	6½ months	OP	3½ years +	4 years +	Paraplegic
10	12 months	OP DXR	14 years +	15 years +	Normal
11	4 months	OP DXR	4¾ years +	5 years +	Working
12	9 months	DXR Drugs	1¼ years	2 years	Dead
13	6 weeks	OP	3 days	6½ weeks	Dead
14	2 years	OP DXR	4 years +	6 years +	Working
15	5 months	OP	4 years	4½ years	Dead
16	3 months	OP DXR	8 years	8¼ years	Dead
17	3 years	OP DXR	3 months+	3¼ years +	Paraparetic
18	2 months	OP DXR	10 months	1 year	Dead
19	2 months	OP DXR	5 months	7 months	Dead
20	6 months	OP DXR	4 months	10 months	Dead

OP = Operation. DXR = Radiotherapy.

received adequate treatment but in 83 only could its results be assessed accurately.

Of the 55 patients who were not treated (including Cases 2 and 3, Table II), 26 were dead within 6 months of the first symptom and all but 4 had died after two years. Several, however, had manifestations of multiple myelomatosis and remained untreated on account of this.

Medical treatment included stilbamidine (Baker and Casterline, 1948: Bichel, 1950, Cases 6 and 9: Layani, Aschkenasy and Nadal, 1952: Greenwald, Bronfin and Auerbach, 1953, Case 1: Case 12), urethane (Rundles and Reeves, 1950), radio-active isotopes (Lawrence and Wasserman, 1950), and spinal supports. Their effects were only palliative but frequently they alleviated pain, as in Case 12.

Surgical treatment.—All but one (Case 12) of the 18 treated patients were operated upon and 12 had radiation therapy besides (Table II). The operation invariably consisted of a laminectomy and in most cases the removal of as much as possible of the myelomatous tissue. Complete extirpation was not always possible owing to inaccessible extensions in the spinal canal, the bone or the paravertebral regions. The immediate results were often dramatic, as in Cases 1, 7, 10, 16 and 17, and the patient of Snyder and Wilhelm (1948), so that cord function returned rapidly and at times completely. In addition, most patients were relieved of pain, either because of removal of the tumour, or section of spinal roots. When cord decompression had been delayed however, recovery, as might be expected, was absent or slight.

Of the 5 patients who had surgical treatment alone, 3 were not treated further because of their poor general condition (Cases 5, 9 and 13) and 2 of them died early in the post-operative period (Cases 5 and 13); Case 9 was the only one made worse by operation. The other 2 (Cases 4 and 15) survived one year at least, and four years respectively. In the literature there were 33 patients who had operation alone and only one-third survived more than three years post-operatively; only one patient lived more than five years. However, the group contained the early deaths following operation as well as those patients manifesting the generalized disease in whom further treatment was deemed unwarranted.

Radiation therapy.—6 patients who received irradiation only, had better survival rates than those treated with surgery alone. 12 of the present group were thus treated after operation (Table II) and there are 42 examples in the literature. Of the latter, only 4 had died in the first two years following treatment and 7 survived more than five years.

Case 10, the solitary epidural myeloma, is excluded from the 12. The average post-operative survival period in the 11 cases was 2·8 years: the fate of 1 patient is unknown, although he was alive three years after operation (Case 1): 5 are still alive (average survival of 3·2 years) and 5 have died (average survival 2·5 years). There seems to be no constant relationship

between longevity and the presence of the generalized disease, but those who are still living have an average total survival of four and a half years whereas in those who died it was three years. It is possible, however, that the disease process was of a more rapidly progressive type in the latter, quite apart from the influence of therapy. 4 of the 5 survivors have returned to work and are in good health, despite the fact that the disease is widespread in 2 of them.

Therapeutic suggestions.—In spinal compression complicating myelomatosis, it is often possible to achieve an amount of improvement unknown to other features of the disease. When recognized, a laminectomy should be carried out as soon as possible, unless of course the disease is well advanced. As much as possible of the tumour should be removed and the area then irradiated. Complete extirpation of the myeloma should be aimed at and even if other evidence of myelomatosis is present, this plan of treatment is not necessarily invalidated. Thus 2 patients (Cases 11 and 14) with generalizations have survived five and six years respectively, since the onset of the disease. The importance of treating these patients with both operation and radiation therapy (Albert, 1951) is illustrated by Case 11 because a recurrence after the first operation did not follow the second which was supplemented by irradiation. One patient (Case 16, fig. 9), after adequate treatment of a spinal myeloma, had an additional five years of useful life before dissemination of the myelomatosis began. Furthermore, in the absence of bone changes, the lesion may be a primary epidural myeloma, in which case the prognosis is excellent (Case 10). Only those patients in whom spinal compression develops late in the course of multiple myelomatosis should be denied active therapy and Svien *et al.* (1953) have recently emphasized this conclusion.

Non-compressing Spinal Cord Lesions

It has been claimed that multiple myelomatosis may be complicated by intrinsic disorders of the spinal cord as well as by spinal compression. Certain authors have suggested that "toxins" produced by myelomatosis may affect the nervous system, and the cord in particular. However, the cases described by Nonne (1921, a and b) and Kreuzer (1926), although frequently cited as examples of this process, probably had spinal compression. Others have evoked "toxins" despite the presence of a spinal myeloma (Pines and Pirogowa, 1928, Case 2: Schluppli, 1939: Hallermann, 1929, Case 8) and it is likely that Sjögren and Wohlfahrt (1933) were describing the results of compression rather than those of subacute combined degeneration of the cord as they thought. Lindeboom and Mulder (1941) report a similar case and Snapper *et al.* (1953, p. 34) mention a "non-specific type of degenerative disease of the spinal cord" occurring with myelomatosis. The grey degeneration of the posterior columns in the

patient of Ellinger (1899) were probably due to neurosyphilis or anæmia, as Magnus-Levy (1932) has suggested.

The evidence concerning indirect involvement of the spinal cord in myelomatosis is thus very slender. Possibly, unlike other malignant diseases, it does not occur, as might be expected from the respect shown to the nervous system by myelomatosis tissue (fig. 3). Similar conclusions concerning the rest of the nervous system have been arrived at (Clarke, 1954).

Summary

Spinal compression of various degrees is a common neurological complication of multiple myelomatosis and occurs in about 20 per cent of cases. Its pathology, clinical picture, radiological and C.S.F. findings are considered, using 20 illustrative cases and 204 from the literature. Frequently the illness begins with cord or cauda equina features due to a spinal myeloma arising from bone (85 per cent); a primary epidural myeloma does, however, exist. In other cases (15 per cent), spinal compression begins after the onset of the generalized disease. In each type treatment should be prompt and adequate, with the aim of total eradication of the compressing mass, first by surgery and then by radiation therapy. Although the overall course of the disease may not be influenced, considerable relief from the features of spinal compression may be obtained and are considered well justified.

The evidence for a "toxic" factor affecting the spinal cord in myelomatosis is reviewed and the conception rejected.

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LEGENDS FOR PLATES

PLATE XXIV

FIG. 2 (Case 13).—Transverse section of cord showing epidural myeloma and thickening of dura mater (x9).

FIG. 3 (Case 13).—Junction between dura mater and myelomatous tissue (x420).

PLATE XXV

FIG. 4 (Case 6).—Radiograph showing myeloma of L3 vertebral body extending into lamina.

FIG. 5 (Case 6).—Radiograph of L3 showing collapse and destruction one and half years later.

PLATE XXVI

FIG. 6 (Case 7).—Myelographic block produced by epidural myeloma at T9. The vertebræ are normal.

FIG. 7 (Case 14).—Erosion of laminæ and posterior part of L1 vertebra.

PLATE XXVII

FIG. 8 (Case 14).—Myelographic block at L2. Paravertebral shadow on right.

FIG. 9 (Case 16).—Radiograph showing appearance of L3 myeloma five years after treatment.

PLATE XXIV

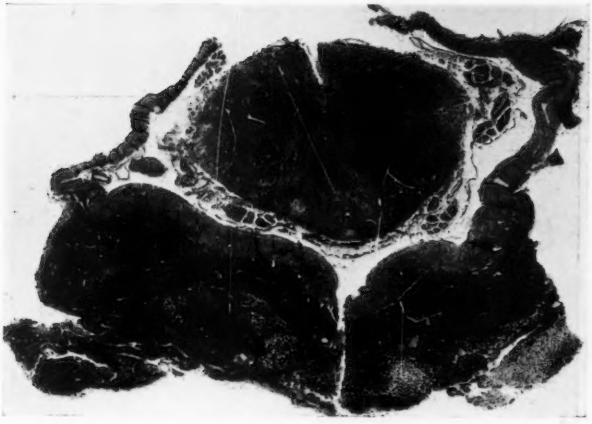

FIG. 2.

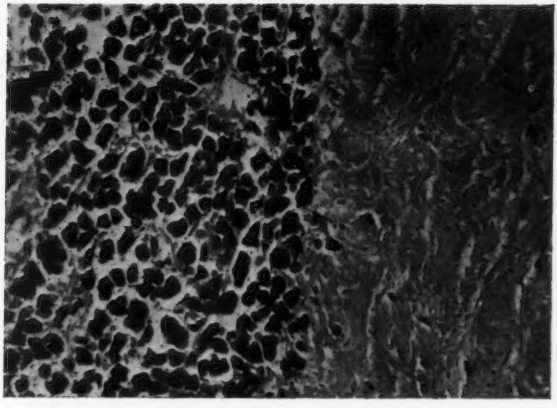

FIG. 3.

To illustrate article by Edwin Clarke.

PLATE XXV

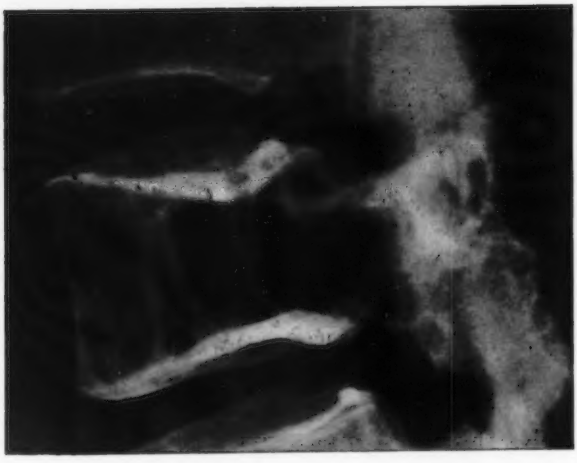

FIG. 4.

FIG. 5.

To illustrate article by Edwin Clarke.

PLATE XXVI

FIG. 6.

FIG. 7.

To illustrate article by Edwin Clarke.

PLATE XXVII

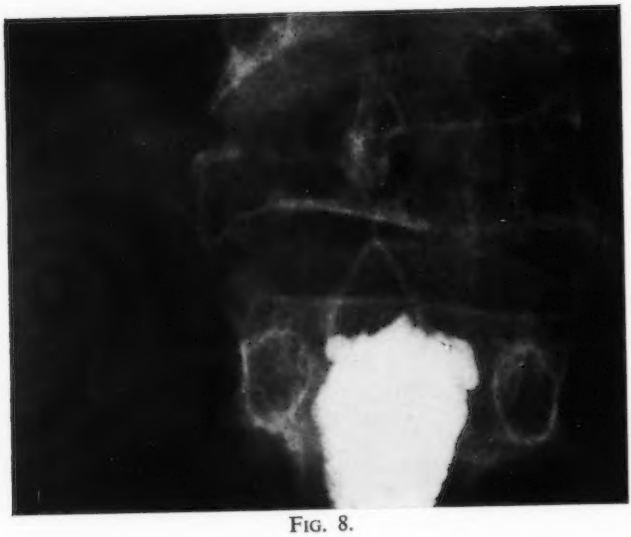

FIG. 8.

FIG. 9.

To illustrate article by Edwin Clarke.

RARE VARIANT OF MYOTONIA ATROPHICA—CLINICAL AND ELECTRO-MYOGRAPHIC STUDY OF A FAMILY

BY

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THE main features of the complex syndrome known as myotonia atrophica are now well defined, if not well understood, and comprise (*a*) myotonia (*b*) muscular atrophy (*c*) a "pluriglandular disorder" of varying manifestations, the most constant being premature baldness and testicular atrophy in the male, and (*d*) lenticular cataract.

The condition is strongly familial and appears dominant (Maas, 1937) and although the exact genetic manner of inheritance is in doubt (Maas and Paterson, 1939; Ravin and Waring, 1939; Tyler, 1954), it is apparent that various fragments of the syndrome can be demonstrated in various members of an afflicted family. In recent years attention has been called to its less well-known manifestations such as colloid goitre (Benda *et al*, 1954; Maas, 1937) disease of cardiac musculature (Fisch and Evans, 1954; Miller and Drew, 1952) and mental deficiency (Maas, 1937).

The present family of cases are reported chiefly because they call to attention two rare variants of the disease which tend to obscure the correct diagnosis. In these individuals myotonia was absent as a symptom, was not found on physical examination and was discovered only by electromyography. Myotonia atrophica in this family was also part of a complex extensive hereditary syndrome with prominent features of central and peripheral nervous system disease—fasciculations, sensory loss, ataxia, pes cavus, scoliosis, stuttering and mental deficiency.

The family pedigree as known is given in fig. 1. All that can be discovered of the generation antecedent to the first severely afflicted one is that the father died at an advanced age of "heart trouble." Of this family two members were carefully studied as hospital patients (P. L. and J. L.) and two more were examined (S. C. and F. L.) more superficially as outpatients. Their case reports are given in some detail because they define this complex familial syndrome with its myopathic, neurologic and endocrinopathic features.

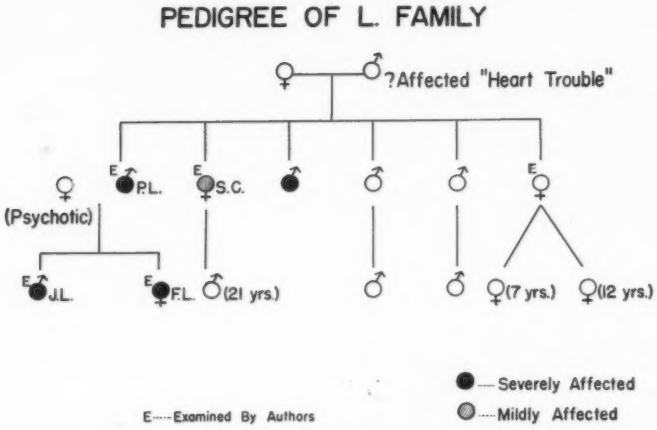

FIG. 1.

Case 1.—P. L. This is a 55-year-old, Russian-born, Jewish male, who remembers weakness in his left leg beginning at age 7, progressing very slowly, and beginning in the other leg in the second and third decades. By the age of 40 both legs were extremely weak in all muscle groups, although he could still walk, and both arms were also severely affected. Fasciculations were noted in all muscles at that time, and have been present constantly since then. Atrophy of all muscle groups in arms and legs was first noted definitely in the third decade and since then has slowly progressed to a severe degree in the distal portions of the extremities. Upon careful questioning, the patient admitted that in his youth his hands would "become somewhat stiff" in cold weather, but no frank myotonia was ever noticed. He has always stuttered on becoming excited.

Since age 40 the patient had had intermittent orthopnœa, paroxysmal dyspnœa and ankle œdema. Systolic blood pressure in the range of 150-160 had been reported. The patient since being confined to a wheel chair had had two periods of thrombophlebitis of the legs.

General physical examination.—The patient is a cheerful, alert, intelligent, cooperative, and moderately emaciated elderly man. The blood-pressure is 150/90. There is almost complete baldness. Examination of the chest reveals a slight dorsal kypho-scoliosis but no other abnormalities. The abdomen is unremarkable. Genitalia are normal in size and there is no perceptible testicular atrophy.

Neurological examination.—Atrophy of all muscle groups of the body is apparent, extreme in the intrinsic muscles of the hands, in the forearms and in the anterior tibial and gastrocnemius groups in the legs. There is slight atrophy of the sternocleidomastoid, masseter and intercostal muscles (fig. 2).

The patient can stand with support but cannot walk. There is slight power remaining in fingers and wrists, somewhat greater strength in the upper arms, but complete paralysis of the calf muscles.

No myotonic phenomena to percussion, repeatedly searched for, has ever been demonstrated on this patient. The characteristic slow relaxation and "stiffening" of the musculature of myotonia is, however, clearly demonstrated after immersion of the forearms in ice water.

Prominent fasciculations are continually seen, both fine and gross, in the fore-

arms and upper arms, occasionally in the hands, in the thighs, and prominently in the pectoral and intercostal muscles. All deep tendon reflexes are absent. Repeated sensory examinations have demonstrated a touch and vibratory sense loss in the feet and hands in a glove and stocking distribution with no consistently reproducible loss to other sensory modalities.

Examination of the cranial nerves revealed the atrophy of masseter and sterno-cleidomastoid muscles, as noted, but was otherwise negative. The patient has a mild stutter, intensified by agitation.

Slit-lamp examination of the eyes revealed early snowflake-like opacities in the posterior portion of both lenses.

Laboratory examination.—Repeated white and red blood count values were within normal limits, as was urinalysis except for one period of urinary tract infection. Serological tests for syphilis were negative.

Values for blood sodium, potassium, calcium, phosphorus, alkaline phosphatases and urea nitrogen were also normal. Fasting blood sugar was 75 mg. per cent. and glucose tolerance test done with 100 gm. glucose orally revealed the following values: 30 minutes—149 mg. per cent, 1 hour—203, 2 hours—121, 3 hours—50, 4 hours—41, 5 hours—59.

Lumbar puncture revealed clear, colourless fluid under no increased pressure, containing 1 lymphocyte, 44 mg. per cent. of protein, and 80 mg. per cent. of sugar. The gold sol curve was normal as was serological reaction for syphilis.

Creatine excretion for twenty-four hours varied from 740 to 1,100 mg., creatinine excretion varied from 890 to 1,100 mg.

X-ray examinations of bones revealed various interesting findings: (*a*) generalized increase in bone density of calvarium, base of the skull and bones of the chest somewhat resembling "marble bones"; (*b*) deformity of the neck of right femur with coxa vara and a congenital variation in the acetabular portion of both iliac bones; (*c*) calcification in the right abdominal gutter, interpreted as being in the area of the right adrenal gland; (*d*) osteo-arthritis of the cervical spine with narrowing of the C 4-C 5 intervertebral disk spaces and posterior spurring. Electrocardiogram was normal.

Twenty-four hour urinary excretion of 17-ketosteroids was 3.66 mg., and of the corticoids 4.6 mg. (Steroid determinations were done by the Laboratory of Dr. Joseph W. Jailer, Columbia College of Physicians and Surgeons.) Radio-active iodine uptake was 29 per cent.

Biopsy taken from the anterior tibial muscle showed almost complete destruction of muscle structure with interruption of individual fibres and loss of cross striations. There were multiple foci of proliferated sarcolemmal nuclei, usually surrounding the fragmented fibres (fig. 3). (Muscle biopsy read by Doctors Robert D. Terry and Harry M. Zimmerman.)

Case 2.—J. L. (son of P. L.). This 31-year-old man had been a patient for several years in a mental institution. Since childhood he had had difficulty raising his feet and had noted slowly progressive atrophy of the muscles of the hands and feet, forearms and lower legs. There was no history of difficulty with muscular relaxation.

Since early adolescence this patient had been extremely seclusive and bizarre in his behaviour. H. attended two years of high school, but at age 16 began to have auditory hallucinations and paranoid delusions. For ten years the patient had been confined in various mental institutions suffering from a schizophrenic psychosis that was mildly and intermittently paranoid in nature.

He had developed marked frontal baldness in his middle twenties; since that age he had noted no sexual desire or erections. Since adolescence he had been very stout.

Physical examination.—The patient was an obese man of 31 with marked concentration of adipose tissue on hips, thighs and thorax. There was moderate gynecomastia, normal distribution and amount of body hair (fig. 4). Testes were very small.

Neurological and ophthalmological examinations.—Moderate weakness of muscle groups in all four extremities was present symmetrically with weakness greatest in the intrinsic muscles of the hands and in the distal musculature of the legs. Muscular atrophy was apparent in all weak muscle groups, to an extreme degree in hands and lower legs. The patient walked with a high-steppage "foot-drop" gait. There was some atrophy of masseter, temporal and sternocleidomastoid muscles. No fasciculations were seen. No myotonia was elicited either by percussion of any muscle or after voluntary contraction.

Deep tendon reflexes were absent in the upper extremities, and in the legs only sluggish knee-jerks were obtainable. There was no other reflex abnormality. There were mild ataxia and intention tremor in both upper and lower extremities.

Sensory examination gave varying findings—it was the opinion of most examiners that there was some diminution of position and vibratory sense in the hands and feet but that other sensation was normal. There was marked stuttering speech, intensified by emotion.

Examination of cranial nerves.—Corrected vision was 15/20 bilaterally, correction being for high myopia. Optic fundi were normal, but, on slit-lamp examination of both eyes, radially arranged wedge-shaped opacities were seen on both surfaces of the nucleus of the lens. There was also a central discoid opacity in the left eye. The only further finding of significance was the atrophy of head and neck musculature noted above.

Laboratory examination.—Blood count and urinalysis were within normal limits. Serological reaction for syphilis was negative. Radio-active iodine uptake was 26 per cent. (normal). Serum sodium was 139-41 meq./L, potassium 4·3 meq./L, 24-hour urinary excretion of 17-ketosteroids was 3·99 mg. of corticoids 4·98 mg.

Oral glucose tolerance test revealed fasting blood sugar—75 mg. per cent., 30 minutes—128, 1 hour—111, 2 hours—53, 3 hours—57, 4 hours—65, 3 hours—69. Other values were Serum CO_2—24 meq./L, Chloride 108 meq./L, Cholesterol—132 mg. per cent., 24-hour creatine excretion—·26 gm., creatine excretion—1·4 gm.

X-ray examination of thorax revealed a moderate dextro-roto-scoliosis of the upper dorsal spine; X-rays of the hands and feet revealed a "bizarre splaying" of the metatarsals and metacarpals. X-rays of the skull were negative.

Testicular biopsy revealed normal Leydig cells; all stages of spermatogenesis were present, but it was felt that sperm were decreased in number. Electroencephalogram was normal.

Psychometric testing revealed that the patient's intelligence was at least on an average level but impaired by emotional disturbance. He achieved high scores in verbal tests and low in abstract social judgment. He had spectacular mathematical ability, and was able, for example, to solve long arithmetic problems correctly without recourse to writing.

This patient became increasingly paranoid while in the hospital and study of his case was interrupted when it became necessary to transfer him to a psychiatric institution.

Case 3.—S. C. This 52-year-old sister of P. L. noted in her middle twenties wasting of the musculature of the hands. There had been no progression in the past ten years. She believed foot deformity had been present since early childhood, but no weakness in the legs had been noticed at that time.

No myotonic difficulty in relaxation had ever been observed. For eight years the patient had suffered from mild diabetes.

Examination revealed a short stout woman with mild weakness of forearm and hand musculature bilaterally. There was slight weakness also of anterior tibial musculature.

Both feet showed pes cavus deformity and the hands showed marked hyperextensibility of metacarpophalangeal joints. There was some staggering on attempt at tandem walking and some ataxia on heel-to-knee test bilaterally, but no incoordination in the upper extremities. All deep tendon reflexes were absent. There was proprioceptive loss in the feet, vibratory sense loss in fingers and toes. The possibility of diabetic neuropathy was of course present. There were no fasciculations, scoliosis, stuttering, and no lenticular cataracts were seen in slit-lamp examination. The patient's diabetes was mild and easily regulated by 5 unit Protamine Zn. insulin daily. The patient was not hospitalized and no further studies were performed.

Case 4.—F. L. This 23-year-old daughter of P.L., since early childhood, has had a bilateral foot deformity, slight weakness of peripheral musculature in all four extremities, moderate mental defect and stuttering. None of these phenomena had been progressive. Her face had always been thin. No myotonia had ever been noticed by the patient or others.

Examination revealed a short (4 ft. 10 in.) stout young woman with obesity confined to trunk and thighs (fig. 5). The gait was "broad-based." There was slight weakness of all finger movements, some weakness of the triceps, hip flexors, quadriceps and anterior tibial muscle groups bilaterally. No definite focal muscle atrophy was seen, except in the face and neck (masseters and sternocleidomastoids). The hands were very small and showed a striking hypotonia at the carpal and interphalangeal joints. There was marked pes cavus foot deformity bilaterally (fig. 6). No fasciculations were seen.

There was a slight tremor of the outstretched arms, somewhat intensified by intention, and succession movements were very poorly performed bilaterally, with evidence of dyssynergia. Stuttering speech was marked. All deep tendon reflexes were absent except for a sluggish left knee-jerk.

Sensory examination revealed absent vibratory sensation in feet, the remainder of the examination being normal.

Slit-lamp examination of the eyes showed numerous fine white dots in the zonular area of both lenses, between the cortex and nucleus.

Electromyographic Data

Adrian and Bronk (1929) coaxial needle electrodes were used with a battery operated pre-amplifier, push-pull throughout, having a frequency response of better than 20-20,000 c/sec. Recordings were made on a Magnacordette tape recorder, at 15 in./sec., played back and photographed on a Dumont Type No. 322, Dual-Beam oscilloscope.

Patient P.L.—On insertion of the needle into the right biceps at rest, the pathognomonic "myotonic" reaction was heard in the loud-speaker and seen on the cathode ray oscillograph. This consists of showers or burst of very brief monophasic or biphasic high-frequency rhythmic discharges, the frequency increasing to a maximum (occasionally as high as 200 per sec.) and then waning, the whole "burst" usually lasting one to several seconds. Duration of the single spikes is not more than 1-2 milliseconds, about the duration of fibrillation

potentials, as pointed out by Landau (1952). The bursts were produced or reactivated by movement of the needle. They produced in the loud-speaker the characteristic dramatic sound which has been likened variously to a dive-bomber, machine-gun, or hail-storm. The myotonic discharges were found in both biceps muscles (fig. 7), and in the markedly atrophic anterior tibial at rest. It is interesting that these muscles are ones in which previous workers have found not "spontaneous" (peripheral) myotonia, but rather myotonia occurring following voluntary contraction or percussion of the muscle (Landau, 1952; Buchthal and Clemmesen, 1941).

In addition repetitive, extremely high-voltage, complex, polyphasic potentials at a much slower rate were recorded at rest from both biceps, both deltoid muscles and from the quadriceps—wherever fasciculations were seen (fig. 8). These were present at all times when the electromyogram was not dominated by the "myotonic" discharge.

Patient J.L.—Electromyography of the atrophied tibialis anticus muscle revealed various findings: (1) the characteristic brief, simple potentials in rhythmic trains or "dive-bomber" effect of myotonia; (2) extremely brief, low-voltage (50-100 μv) potentials appearing on insertion and resembling fibrillation; (3) normal biphasic potentials; (4) polyphasic potentials similar to those seen on his father. These findings were unfortunately not recorded, but all of them with the exception of the fibrillation potentials were found in this patient's father, P.L.

Patients S.C. and F.L.—Examination of several muscles revealed no myotonia or other abnormal potentials, either at rest, during muscular contraction or on relaxation.

Discussion

The family shows many of the familiar manifestations of myotonia atrophica. The slowly progressive muscular wasting, continuing through adult life, occurring chiefly in the distal parts of the extremities, in the neck, and in the face is characteristic, as is the early baldness occurring in father and son, testicular atrophy in the son and the posterior lenticular cataracts seen in the father and two children without clinical manifestations.

Mental deficiency, seen in F. L., occurs frequently in children of families afflicted with myotonia and is apparently a part of the more severe disease, as it is seen in succeeding generations. The presence of mental defect certainly suggests, as do the observations below, that the myotonia dystrophica syndrome may incorporate central nervous system disease. The schizophrenic psychosis of J. L., however, probably was related to the fact that his mother, his maternal aunts and grandmother had all suffered from a similar psychosis.

Endocrine abnormalities were confusing in these cases, as is common in this disease (Benda *et al.*, 1954). In P. L. there was no evidence of endocrine dysfunction save for low 17-ketosteroid excretion. J. L. had small testicles, gynecomastia, diminished excretion of 17-ketosteroids, hypoglycæmia, all except the latter possibly attributable to testicular atrophy. Certainly there was no clearcut evidence of pituitary hypofunction despite the patient's appearance.

Myotonia to percussion and myotonic delay of muscle relaxation is, of

course, the hallmark of the syndrome and occurs characteristically in the thenar, tongue and forearm muscles. The fact that the phenomenon varies from time to time (being intensified for example by cold and emotion) has been stressed, and the occasional absence of the phenomenon has been noted (Adie and Greenfield, 1923; Coers, 1952). It has been particularly noted that myotonia often cannot be elicited from atrophied muscles. The present family appears unique, however, in that myotonia to percussion or after contraction was never elicited from any muscles in the four members of the family examined, all of whom had varying degrees of muscle atrophy. Only P. L., the most severely afflicted, admitted to direct questioning that his hands would "stiffen up" on exposure to cold; myotonia was demonstrated after contraction in this patient only after exposure of the hands to ice water.

The electromyographic pattern of myotonia in P. L. and J. L. with the muscle at rest and in relaxation after contraction were diagnostic—the high-frequency rhythmic trains of narrow spikes that waxed and waned giving the characteristic "dive-bomber" sound on the loud-speaker. Several studies have pointed out the specificity of this electromyographic pattern, although whether the origin of the potential is totally intramuscular and whether it contains an element of reflex muscle contraction is debated (Landau, 1952; Denny-Brown and Nevin, 1941; Shea *et al.*, 1952; Coers, 1952).

There are several indications in the family reported here that the myotonia dystrophica is accompanied by some nervous system disease. Fasciculations were prominent clinical phenomena in P. L. and were shown to have the characteristic polyphasic pattern by electromyography. True fasciculations as seen clinically probably occur only in disease of the spinal cord, anterior root, or less commonly, of the peripheral nerve. It should be noted, however, that almost simultaneous discharging of two or more myotonic spikes may occur, occasionally leading to trains of polyphasic potentials (Coers, 1952; Lefevre *et al.*, 1947). It is conceivable that such polyphasic potentials of muscular origin could be accompanied by clinical fasciculations in the absence of nervous system disease.

Certain electromyographic patterns seen in the biceps and other muscles of P. L. at rest are peculiar in several respects and their nature and origin are doubtful. Their amplitude is abnormally high (up to 2-3 millivolts) and their shapes vary in a continuum of patterns from the very brief narrow potentials described in muscular dystrophy (Pinelli and Buchthal, 1953) to the extreme polyphasic pattern described in fasciculations. Which of these patterns are myogenic and which neurogenic is difficult to ascertain.

There were here, however, other prominent signs of a familial disease of the neuraxis. The whole family suffered from various degrees of pes cavus foot deformity—one of the cardinal signs of the hereditary ataxic diseases of the nervous system

The scoliosis seen in P. L. and J. L. is also probably a part of this familial disease complex, as it is commonly seen in association with, e.g. Friedreich's ataxia and hereditary spastic diplegia, but rarely as a part of a muscular dystrophy syndrome (Mackay, 1954). The hyperextensibility of the joints seen prominently in J. L., and F. L., was also probably a congenital anomaly of the type seen in "heredo-degenerative" neurological disease. This association of myopathy, myotonia and heredo-degenerative disease of the nervous system has been reported recently (Stevens, 1954) as a familial syndrome; in the latter, however, most of the features of myotonia atrophica were absent and periodic paralysis was part of the syndrome.

All members of the family here reported showed defective vibratory sensation in the extremities. This phenomenon is interesting in view of the fact that Stewart in 1909 (referred to by Adie and Greenfield, 1923) originally described dorsal nerve root degeneration in an autopsy of a patient with myotonia atrophica but these changes were attributed to coincident tabes dorsalis, and sensory abnormalities have apparently been reported by only one observer since (Maas, 1938).

Summary and Conclusions

(1) A family is reported in which all of the manifestations of myotonia atrophica except myotonia were seen in varying degree of severity and completeness, in different members of two generations. Clinical myotonia was, however, seen in only one patient, and then only after exposure of an extremity to severe cold.

(2) Electromyographic examination of muscles of two patients at rest showed the typical "dive-bomber" myotonic potentials despite the absence of clinical myotonia.

(4) An unusual neurological syndrome also occurred in the family—characterized by peripheral sensory loss, pes cavus, scoliosis, stuttering, mental deficiency, hyperextensibility of the joints and, in one patient, fasciculations.

(4) The unusual character of the electromyographic data is emphasized—the high voltage of the potentials and the difficulty in determining whether certain of the complex potentials were myogenic or neurogenic or a combination of the two.

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PLATE XXVIII

FIG. 2.

To illustrate article by Dewey K. Ziegler and Joseph Rogoff.

PLATE XXIX

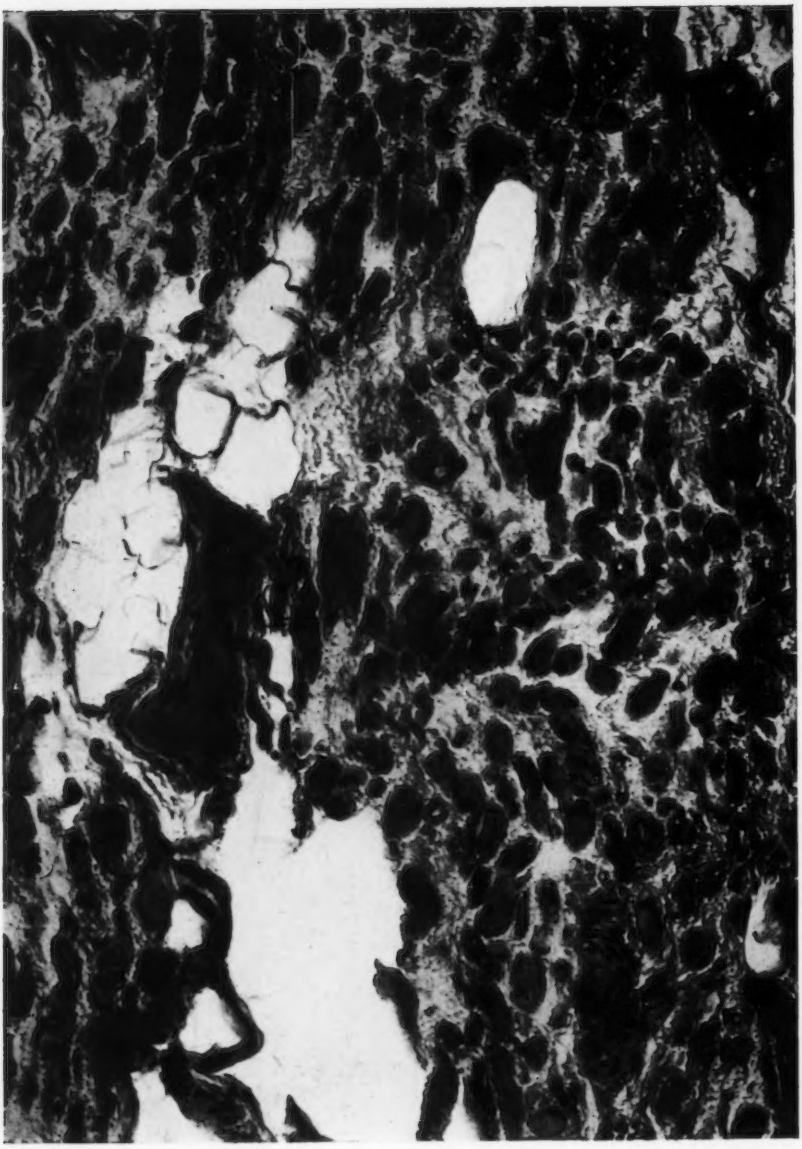

FIG. 3.

To illustrate article by Dewey K. Ziegler and Joseph Rogoff.

PLATE XXX

FIG. 4.

FIG. 5.

To illustrate article by Dewey K. Ziegler and Joseph Rogoff.

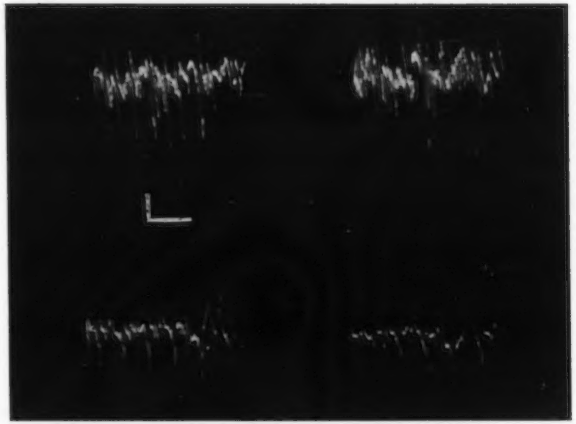

FIG. 7.

FIG. 6.

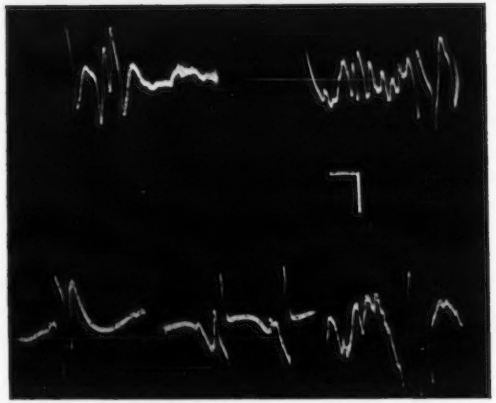

FIG. 8.

To illustrate article by Dewey K. Ziegler and Joseph Rogoff.

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LEGENDS FOR PLATES

PLATE XXVIII

FIG. 2.—P. L., aged 55.

PLATE XXIX

FIG. 3.—Anterior tibial muscle of P. L. showing destruction of muscle fibres and proliferation of sarcolemmal nuclei H. and E. × 230.

PLATE XXX

FIG. 4.—J. L., aged 31.

FIG. 5.—F. L., aged 23.

PLATE XXXI

FIG. 6.—Left foot of F. L. illustrating familial pes cavus.

FIG. 7.—Electromyographic records of myotonic discharge in resting muscles of P. L.
Upper — Right biceps.
Middle — Calibration, 500 microvolts, 16 milliseconds.
Lower — Left biceps.

FIG. 8.—Electromyographic records probably corresponding to fasciculations in resting muscles of P. L.
Top — Right biceps.
Middle — Calibration, 500 microvolts, 16 milliseconds.
Lower — Left biceps.

To illustrate article by Dewey K. Ziegler and Joseph Kogoff.

FUNCTION OF CORPUS CALLOSUM IN INTEROCULAR TRANSFER

BY

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THE crossed optic fibres may be destroyed in the cat by mid-line section of the optic chiasma. The two eyes then discharge separately into opposite halves of the brain over the surviving uncrossed fibres. Such cats are able to perform with one eye simple pattern discriminations learned with the other eye (Myers, 1955). This interocular transfer in the absence of the crossed optic fibres requires a neural interaction across the mid-line.

The fibre pathways mediating this effect are unknown. From anatomical considerations one would suspect the corpus callosum of subserving an integrative function of this nature and the present investigation was designed to explore this possibility by extending the transfer tests to cats with destruction of both the corpus callosum and the crossed optic fibres.

METHODS

Surgical techniques.—Section of the optic chiasma was effected through a transbuccal approach as previously described (Myers, 1955). For division of the corpus callosum a large unilateral bone flap was removed by the use of a dental crown saw and the bone overlying the superior sagittal sinus was chipped away with bone forceps. The dura was opened to the mid-line and one or two cortical veins were ligated at their entrance into the superior sagittal sinus. With the exposed hemisphere retracted laterally the corpus callosum was carefully divided with the aid of a binocular dissecting microscope. The hemisphere was then gently restored to its former position and the dura laid over the cortical surface. The bone flap was replaced and the muscle and skin layers reapposed with catgut sutures. Post-operative course in all cases was uneventful.

Training and testing procedures.—Transfer of four different discrimination problems was studied. The test patterns used are illustrated in fig. 1. The same training box and procedures were used as described earlier (Myers, 1955). In establishing a discrimination, the two patterns

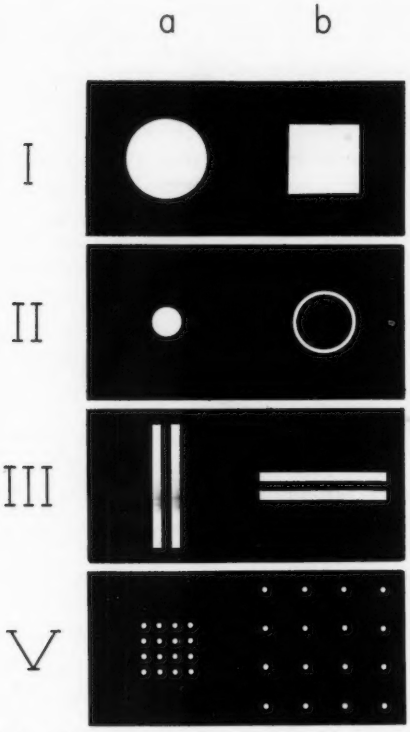

FIG. 1.—Pairs of test patterns used. The discrimination tasks are listed with the positive pattern first. For example, in discrimination I-ab, the positive pattern would be a circle and the negative a square.

of a pair were presented side by side, and the cat was trained to choose one of the two. The patterns were alternated from side to side according to a change sequence. During the periods of training light was excluded from one eye by the use of a black rubber mask held snugly in place by ties to a leather collar. After a cat attained a performance of 34 trials or more correct out of 40 the response was stabilized by giving approximately 400 overtraining trials run in sessions of 40 per day. An exception was *Brd* who was run 920 overtraining trials on problem I-ab. Following the overtraining, tests for interocular transfer of the discrimination were made by shifting the mask to the trained eye for 40 test runs with the untrained eye.

Six cats were used. Four of them were taught two discriminations, one to each eye, and, in these instances, overtraining was carried out with both of the discriminations before any tests were made for transfer.

The problems learned by each cat and the eye initially trained on all discriminations are shown in Table I. In all, transfer tests were made on a total of ten discrimination habits.

TABLE I

INTEROCULAR TRANSFER IN CATS WITH OPTIC CHIASMA AND CORPUS CALLOSUM SECTIONED

Cat	*Eye trained*	*Discrimination*	*Number correct on final 40 overtraining trials*	*Number correct on 40 test trials with untrained eye*
Slv	R	I-ab	40	20
Mmm	R	III-ba	40	20
	L	II-ab	38	19
Brd	R	I-ab	40	13
	L	III-ba	40	20
Knt	R	II-ab	35	19
	L	III-ab	40	20
Bgw*	L	V-ab	40	34
Hnr	R	V-ab	40	28
	L	III-ab	40	20

*Prior experience with discrimination II-ab.

OBSERVATIONS AND COMMENT

The results obtained on the 40 transfer trials run with the untrained eye are listed in the last column of Table I. It may be seen that the performances dropped from the high level attained on the overtraining trials (40 correct out of 40) to a near chance level on the transfer trials (20 correct out of 40). In two instances, however, the performance was significantly above chance, and, in a third, it was significantly under chance. These exceptions are discussed separately below. Among the remaining seven discriminations, deviations from chance were unexpectedly small. This may be attributed to the strong tendency of the cats to revert to a position preference on the transfer trials. Such position preferences are also commonly exhibited when a cat is first presented with a new problem.

Brd, the first of the three exceptional cases, performed only 13 correct out of the 40 test runs with discrimination I-ab. This indicates not only lack of transfer but reveals also a definite preference for the negative pattern. This preference was likely due to some resemblance between this pattern and those of discrimination III-ba previously established with the same eye.

Bgw transferred discrimination V-ab. However, this cat had already been taught discrimination II-ab as part of another investigation. The positive transfer in this case may have been due in like manner to generalization effects arising from an unsuspected similarity between the patterns of the two discrimination tasks. This interpretation was strongly supported when subsequent work with another cat showed a 100 per cent generalization from discrimination II-ab to discrimination V-ab. The cats were presumably responding to some general feature of these patterns like smallness versus largeness or concentration versus diffuseness.

Though *Hnr* performed at a chance level on one discrimination (III-ab), on the second (V-ab) his performance was better than chance (28/40). Figural equivalence effects may again have accounted for the partial transfer although these figures have not been actually tested in this respect. That the transfer was due to effects other than a central neural interaction is strongly indicated, however, by the great ease with which *Hnr* was thereafter taught the inverse discrimination, V-ba, with the untrained left eye. Furthermore, this learning of inverse discrimination V-ba by the left eye resulted in absolutely no disruption of performance on discrimination V-ab with the right eye, contrary to what is seen under the same circumstances in cats with intact corpus callosum. Cat *Mmm* also showed no interference effect when the two eyes were taught inverse discriminations (III-ab and III-ba).

In view of the foregoing it was concluded that the above-chance performances obtained with cats *Bgw* and *Hnr* were a result of irrelevant stimulus generalization effects and did not constitute true exceptions to the lack of interocular transfer seen in the other cases.

The brains of the 6 animals used in this study were examined following formalin fixation. Division of the corpus callosum was found to vary from complete section exclusive of the anterior commissure in *Brd* to section of the posterior two-thirds (12 mm.) in *Mmm*. Varying fragments of the hippocampal commissure were sectioned along with the corpus callosum posteriorly where the two structures lie in close apposition. The mid-line section of the optic chiasma was complete in each case as determined by gross or microscopic examination.

Discussion

Clinical studies have failed to reveal clear-cut alterations in patients with surgical section or pure agenesis of the corpus callosum. Specifically, practic and graphic employment of the two sides of the body is well preserved or normally developed. Visual and tactile gnosis seems also to be unaffected as tested bilaterally, though Maspes (1948) has reported imperfect symbolic recognition in the left homonymous visual fields. Deficits seem to develop only with pathological involvement of one or the other hemisphere. (*See* the reports of Akelaitis, 1941; Akelaitis,

1943; Bruce, 1890; Bunts and Chaffee, 1944; Cameron, 1917; Dandy, 1936; and Smith, 1947.)

Our results in the cat appear, on the other hand, to demonstrate an important integrative function for the corpus callosum. After callosal section there was failure to transfer simple visual problems. Furthermore, completely conflicting problems could be learned with the two eyes without indication of interference implying independent functioning of the two hemispheres in visual learning and recall. These results are in direct contrast with the results obtained in cats with intact corpus callosum (Myers, 1955).

Destruction of the corpus callosum results in a similar disruption of interhemispheric interaction in the cutaneous (Bikov, 1924) and auditory (Stewart and Ades, 1951) spheres. These results with the three most highly developed of the exteroceptive senses suggest a general participation of the corpus callosum in integrating the activity of the two hemispheres in perceptual or cognitive functions.

This raises the problem as to why deficiencies in perception and cognition were not found in the human subjects lacking the corpus callosum if this structure serves such a seemingly important correlative function. Evidence has been presented which indicates that the visual mechanisms on the two sides of the brain are competent although independent in these capacities in the absence of the corpus callosum. Preservation of visual (and tactile) gnosis in the two half-fields following callosal section may then be related to bilateral establishment of experiential effects such as might occur through the corpus callosum prior to section, or, alternatively, through the bilateral projection of the sensory data as occurs with the shifting of the gaze, examination with the hands, and the like. A crucial test of this interpretation has yet to be made in the human. Such a test would involve presentation of novel objects or perceptual problems to one half-field with testing of recognition of the same in the other half-field.

The status of the findings relative to co-ordination within the motor sphere and the transfer of motor learning seems at variance with the findings on perceptual transfer. Bilateral participation in skilled motor performance is unaffected by callosal section (Hartmann and Trendelenburg, 1927). Personal observations of numerous cats and monkeys with total callosal section has also failed to reveal any apparent immediate or long-term deficits in eye-hand co-ordination, skilled manipulatory movements or the like. Ades and Raab (1946) studying reorganization of neuronal mechanisms on the two sides of the brain of the monkey following unilateral removal of the motor area found that the contralateral rearrangement occurred with or without the corpus callosum. Smith (1947) found transfer of non-visual stylus-maze performances from one hand to the other in both the normal and the epileptic with callosal

section. Such evidence suggests bilateral integration of these activities through commissural systems at levels below the corpus callosum.

SUMMARY

The afferent connexions from the two eyes were restricted to the ipsilateral brain-halves in 6 cats by surgical section of the crossing fibres in the optic chiasma. This was followed by sagittal transection of the corpus callosum. These cats were then trained to perform pattern discriminations with a mask covering one or the other eye. When a consistently high level of performance had been attained, the mask was shifted to the other previously unmasked eye whereupon the performance dropped abruptly to a chance level with seven of the ten discriminations tested. The three deviant results were attributable to irrelevant generalization effects between the several discriminations taught the separate eyes. These present findings are in marked contrast with the high level transfer obtained with the corpus callosum intact.

Two of the cats were subsequently taught completely conflicting discriminations with the two eyes. The learning with the second eye occurred with relative ease and resulted in no disturbance in performance with the first eye. This also contrasts with the performances of cats with intact corpus callosum. These results demonstrate the importance of the corpus callosum in the integration of the two hemispheres in visual learning and transfer.

ACKNOWLEDGMENTS

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A STUDY OF THALAMO-STRIATE RELATIONS IN THE MONKEY

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Introduction

THE nuclei of the mammalian dorsal thalamus may be grouped into two functionally distinct systems: a phylogenetically old group of nuclei situated adjacent to the midline and within the internal medullary lamina, and a phylogenetically more recent group of nuclei which have developed *pari passu* with the cerebral cortex. The organization of the latter system has been thoroughly elucidated by the experimental work of Le Gros Clark (1932, 1935) and Walker (1934, 1938b). Although the nuclei of the midline show a progressive regression in ascending phylogeny, the intralaminar nuclei, with one notable exception, are all clearly distinguishable throughout the mammalian series. Their apparent regression in Primates is, in reality, due to the unparalleled development of the principal nuclei. The only nucleus which does not accord with this generalization is the centromedian which shows a precocious development in Primates.

The discovery that most of the midline and intralaminar nuclei have a direct projection to the corpus striatum (Droogleever Fortuyn, 1953; Powell and Cowan, 1954) makes it clear that the neostriatum, like the neocortex, is a morphological and functional dependency of the thalamus. Although this has long been postulated on the basis of comparative studies of the fore-brain, no comprehensive investigation of the thalamo-striate system has yet appeared.

In the present study the organization of the thalamo-striate projection has been investigated in the macaque monkey by the technique of retrograde cell degeneration. A preliminary account of the findings has already been given (Powell and Cowan, 1955).

Material and Methods

Twelve macaque monkeys of different ages were used. In the first four experiments the head of the caudate nucleus was approached through an opening in the anterior horn of the lateral ventricle after raising a bi-frontal osteoplastic flap. The definitive lesion was produced by sucking out varying amounts of the striatum. In two of these experiments the tip of the aspirator was thrust through the septum lucidum into the caudate

nucleus of the opposite side. In the remaining experiments electrolytic lesions were placed in the basal ganglia and adjacent structures by inserting an insulated electrode through a small burr hole in the skull with the aid of a stereotaxic instrument. In three of these animals bilateral lesions were placed. The monkeys were allowed to survive for periods ranging from five to eighteen weeks, after which the brains were removed and fixed in 70 per cent alcohol and 2 per cent acetic acid. Blocks containing the basal ganglia, thalamus and hypothalamus of both sides were embedded in paraffin and sectioned coronally at 25 μ. Every fifth section was serially mounted and stained with thionine; where necessary, a more complete series was prepared.

In the description of the experimental material the two hemispheres of a bilateral experiment will be described separately (and not necessarily consecutively). In such cases the right and left hemispheres are indicated in the text by the suffixes R and L respectively. Unless otherwise stated, nuclei not mentioned in the description of the thalamic degeneration have been found to be normal.

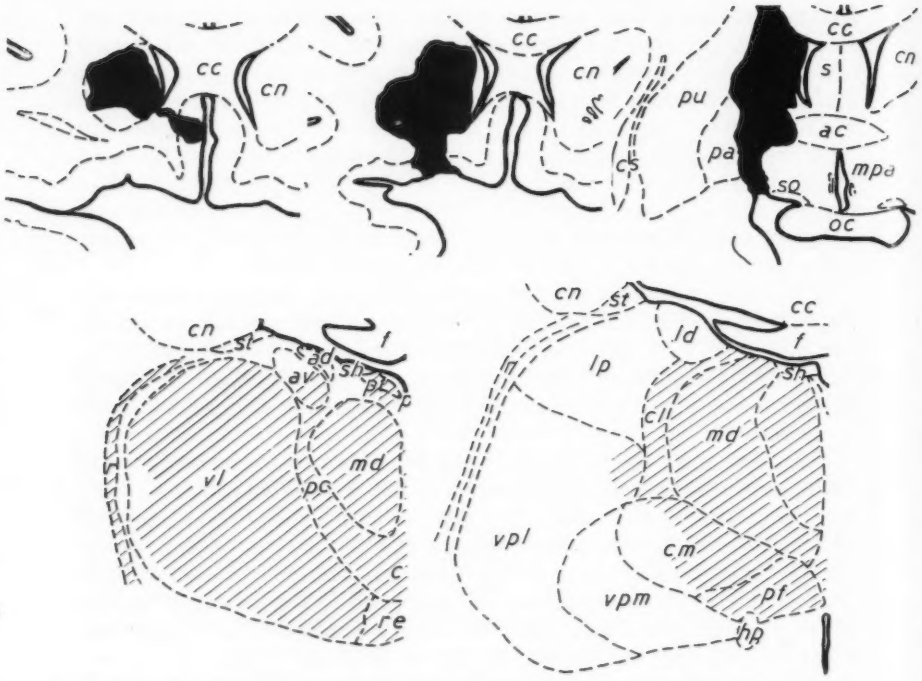
The term "intralaminar nuclei" as used in this paper refers only to the nuclei centralis medialis, paracentralis, centralis lateralis, parafascicularis and the centromedian nucleus. Under the "midline nuclei" are included only the nuclei parataenialis, reuniens, and the anterior and posterior paraventricular nuclei. The nuclei ventralis anterior and the thalamic reticular nucleus are each considered independently of these two groups of nuclei. Striatum is here taken to mean only the caudate nucleus and putamen, and does not include the globus pallidus.

RESULTS

Experiment 1 (MI. 4).—Post-operative survival seven and a half weeks.

A large lesion placed in the striatum and internal capsule rostral to the thalamus has resulted in complete degeneration of nearly all dorsal thalamic nuclei.

The lesion commences at the anterior end of the caudate nucleus, and destroys the entire striatum and internal capsule back to the level of the rostral end of the septum. Ventrally it extends through the nucleus accumbens to reach the base of the hemisphere where it has destroyed the lateral part of the olfactory tubercle. Behind this level the lateral two-thirds of the putamen, although not directly involved, has been completely isolated by the internal capsular lesion. The lateral margin of the lateral septal nucleus and the horizontal limb of the nucleus of the diagonal band have been damaged for a small part of their antero-posterior extent. At the level of crossing of the anterior commissure, in addition to the striatal damage the lesion has destroyed the lateral preoptic area, together with the medial segment of the pallidum, and the lateral margin of the supra-optic nucleus. At this level the medial preoptic area has escaped damage. Further caudally the lesion is restricted to the body of the caudate nucleus and the superior thalamic radiation dorsal to the thalamus as far back as the rostral end of the lateral geniculate nucleus. It should be emphasized, however, that at no point does the lesion directly involve the thalamus, and with the exception of the supra-optic nucleus, the hypothalamus is intact (text-fig. 1).

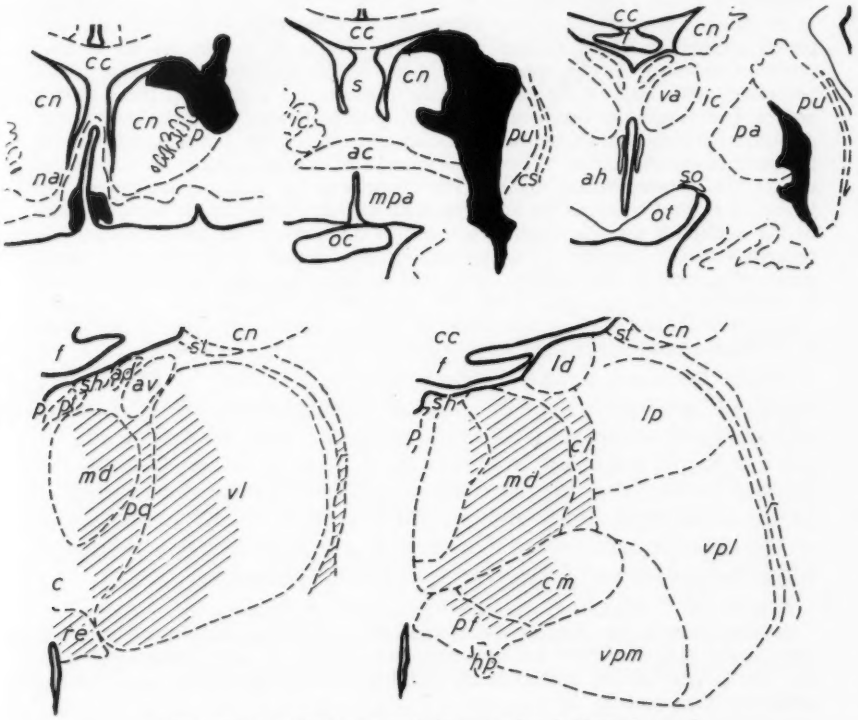


TEXT-FIG. 1.—Diagram showing the site and extent of the lesion and the resulting retrograde cell degeneration in the thalamus in Experiment 1. In this and the succeeding figures the lesion is shown in black and the degeneration indicated by hatching.

Severe retrograde cell degeneration is found throughout the thalamus of the operated side affecting all the midline and intralaminar nuclei and most of the principal nuclei (text-fig. 1). The only nuclei of the former group which have not completely degenerated are the two paraventricular nuclei and the centromedian nucleus. In both the anterior and posterior paraventricular nuclei a few shrunken cells remain along the entire dorso-medial margin of the thalamus. Anteriorly only the ventro-lateral margin of the centromedian nucleus is unaffected, but in the middle third of its antero-posterior extent the ventro-lateral half of the nucleus contains a large number of normal cells; posteriorly only the dorso-medial part of the nucleus is degenerated. The adjacent parafascicular nucleus is completely degenerated throughout. In the principal nuclei normal cells are found in the lateral half of the anteroventral nucleus, the postero-lateral part of the nucleus ventralis lateralis, nucleus lateralis dorsalis, the posterior part of the nucleus lateralis posterior and in most of the nucleus ventralis posterior. The pulvinar and the medial and lateral geniculate nuclei are unaffected. It may be noted that the mediodorsal nucleus is completely degenerated, including the medial magnocellular portion. In the rostral third of the reticular nucleus there is only an occasional cell persisting, but more caudally the nucleus is normal.

Experiment 2 (MI.12R).—Post-operative survival fourteen weeks.

The lesion in this experiment, although involving most of the striatum rostral to the thalamus, is somewhat more restricted than in the previous monkey. The significant thalamic degeneration is likewise similar in extent, but not in severity (text-fig. 2).



TEXT-FIG. 2.—The lesion and degeneration in Experiment 2.

Apart from its anterior extremity, most of the dorsal two-thirds of the head of the caudate nucleus in front of the anterior commissure has been destroyed together with the dorsal half and lateral margin of the corresponding part of the putamen. Ventrally the lesion extends as a narrow track lateral to the putamen to reach the base of the hemisphere, destroying the lateral half of the olfactory tubercle. The ventral limit of the lesion further caudally is indicated by slight damage to the middle third of the alveus on the upper surface of the hippocampus. At the level crossing of the anterior commissure the principal damage is to the medial part of the putamen, the lateral surface of the caudate, and the intervening segment of the internal capsule. Behind this level the lesion gradually diminishes in size, until at the rostral end of the thalamus only the ventro-medial angle of the putamen and the lateral part of the globus pallidus are involved. This part of the putamen is damaged as far caudally as the level at which the lateral geniculate nucleus first makes its appearance.

The thalamic degeneration involves to a varying degree most of the midline and intralaminar nuclei. The nucleus reuniens is almost totally degenerated, only a few shrunken cells persisting throughout its antero-posterior extent. The nucleus centralis medialis is virtually devoid of cells in its dorso-lateral two-thirds, but the ventro-medial margin of the nucleus is quite well preserved. The nucleus paracentralis has undergone complete retrograde degeneration but in the nucleus centralis lateralis a small number of apparently normal cells persist, especially in its caudal part. At its rostral extremity the centromedian nucleus has completely degenerated, but further posteriorly—about the middle of its antero-posterior extent—only the medial two-thirds of this element, together with the adjoining lateral half of the parafascicular nucleus, are affected; at the posterior end of these nuclei the degeneration is even more restricted, being confined to the dorso-medial one-third of the centromedian nucleus and the dorso-lateral half of the parafascicular nucleus. There is no significant change in either the paratænial or the two paraventricular nuclei. The changes in the reticular nucleus of the thalamus parallel those in the adjacent main nuclei. Thus the entire rostral end of the nucleus is severely degenerated, but at the level of the rostral end of the nucleus ventralis lateralis the dorsal half of this element is spared, while more posteriorly, towards the caudal end of the ventralis lateralis, the entire nucleus is intact. Of the principal nuclei the nucleus ventralis anterior, the antero-medial, the medial part of the ventralis lateralis, the ventro-lateral two-thirds of the mediodorsal nucleus are all severely affected.

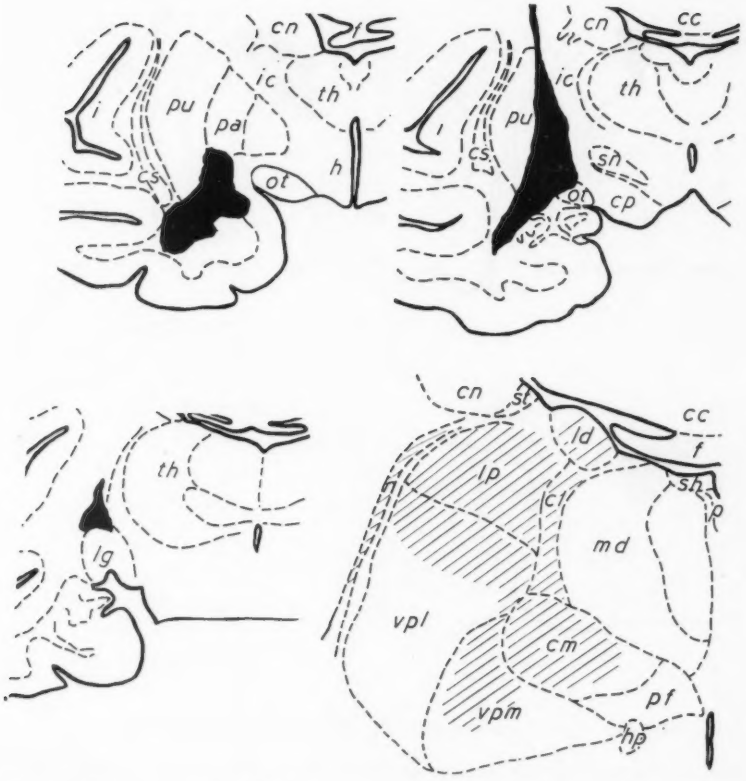
In the following series of eight experiments, it will be shown that retrograde degeneration in the centromedian and parafascicular nuclei only occurs after lesions involving the putamen. That this degeneration is not due to the coincident involvement of other structures (notably the caudate nucleus and internal capsule) will be demonstrated in another section of the paper. Furthermore, it will be apparent from the descriptions of the different experiments that there is a precise spatial organization within the projection of these two nuclei to the putamen.

Experiment 3 (M1.11).—Post-operative survival seventeen weeks.

A large lesion in the globus pallidus and internal capsule, isolating the posterior part of the putamen from the thalamus, has resulted in severe degeneration in the caudal part of the centromedian and the surrounding lateral and posterior nuclear groups (text-fig. 3).

The lesion commences at the tip of the inferior horn of the lateral ventricle, in the dorsal part of the hippocampus. In sections through the rostral end of the thalamus it extends dorsally into the globus pallidus along the medial margin of the putamen. Further caudally it increases in size and, in addition to completely destroying the globus pallidus, it isolates the putamen from the internal capsule and thalamus. A dorsal extension of the lesion reaches through the internal capsule towards the body of the caudate nucleus involving the whole medio-lateral extent of the capsule and the margin of the reticular nucleus at the level of the middle of the nucleus centralis lateralis. At the appearance of the centromedian nucleus the extent of the damage is minimal, and restricted to the dorsal part of the internal capsule and the inferior border of the body of the caudate nucleus as far back as the posterior end of the lateral geniculate nucleus. The anterior two-thirds of the geniculate and the dorso-lateral part of the hippocampus have also been destroyed.

There is no evidence of retrograde degeneration in the thalamus rostral to

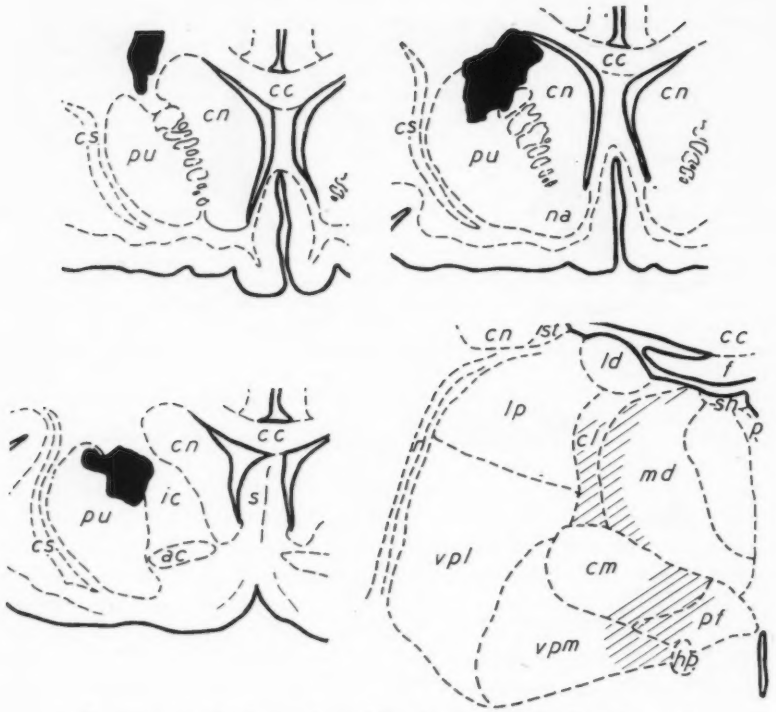


TEXT-FIG. 3.—The extent of the lesion and thalamic degeneration in Experiment 3.

the centromedian nucleus, and in the anterior third of this nucleus only slight gliosis has occurred. In the posterior part, however, there is an increasing amount of degeneration which involves all except that portion of the nucleus adjoining the intact parafascicular nucleus. The only other element in this group in which degeneration is seen is in the extreme caudal portion of the nucleus centralis lateralis in which there is a partial cell loss. The main nuclei involved are the lateralis posterior-pulvinar complex and the intermediate part of the nucleus ventralis posterior.

Experiment 4 (MI.13L).—Post-operative survival six weeks.

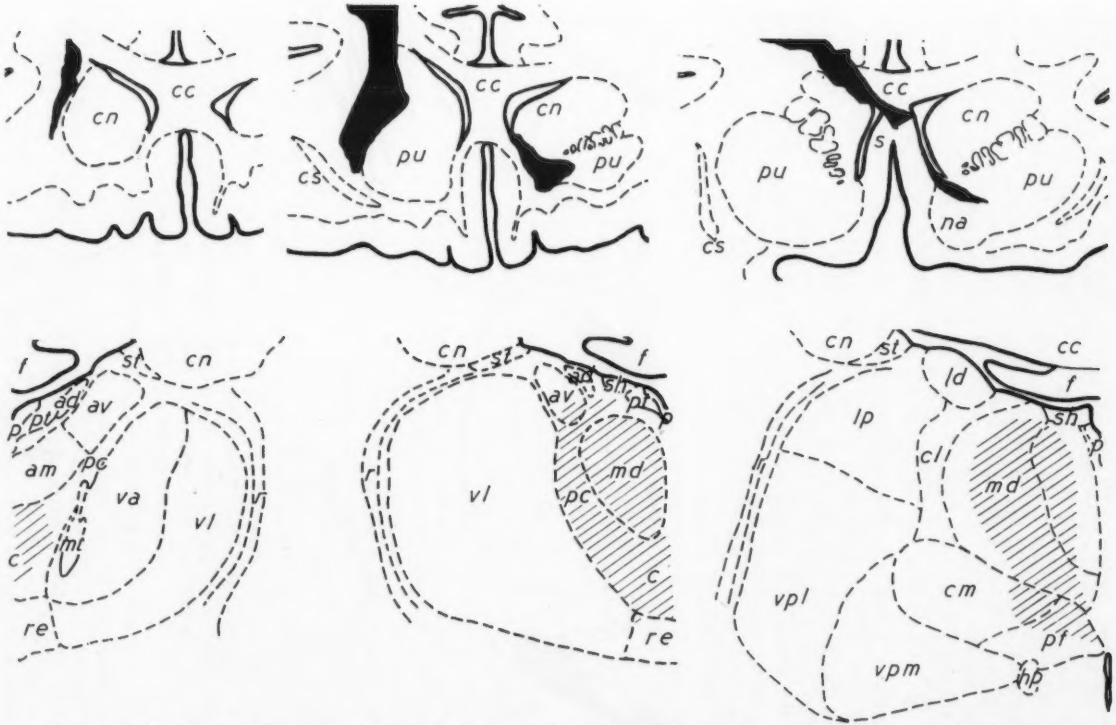
A small lesion, confined to the upper surface of the putamen and which reaches across the internal capsule to involve the dorso-lateral margin of the head of the caudate nucleus, has resulted in a relatively localized degeneration of the centromedian nucleus, nucleus centralis lateralis and the nucleus paracentralis (text-fig. 4).



TEXT-FIG. 4.—Lesion and resulting degeneration in Experiment 4.

The striatal damage commences at about the middle of the antero-posterior extent of the head of the caudate nucleus. At this level the dorso-lateral corner of the caudate and the dorso-medial angle of the putamen, together with the intervening internal capsule, have been destroyed by a small electrolytic lesion. The extent of this damage is more or less constant back to the level of junction of the anterior and middle thirds of the septum, behind which the caudate nucleus and the internal capsule are intact, and the lesion in the putamen somewhat larger. This damage, in turn, diminishes in size and ends immediately behind the level of the interventricular foramen. Extending caudally behind the lesion is a band of dense gliosis which comes to occupy a progressively inferior position in the internal capsule, until at the level of the thalamus it is confined to the region of the inferior thalamic radiation.

The most significant degeneration in the thalamus is in the intralaminar group of nuclei. Of these, the lateral wing of the paracentral nucleus shows evidence of cell loss and gliosis in its posterior half, while the nucleus centralis lateralis is severely affected throughout its entire extent. Only in the dorsal part of the latter nucleus does an appreciable proportion of normal cells persist. In the nucleus centralis medialis there is some cell shrinkage and a slight cell loss in the ventro-lateral part of its cross-sectional area. The centromedian nucleus shows localized degeneration in its medial part, especially anteriorly where almost half

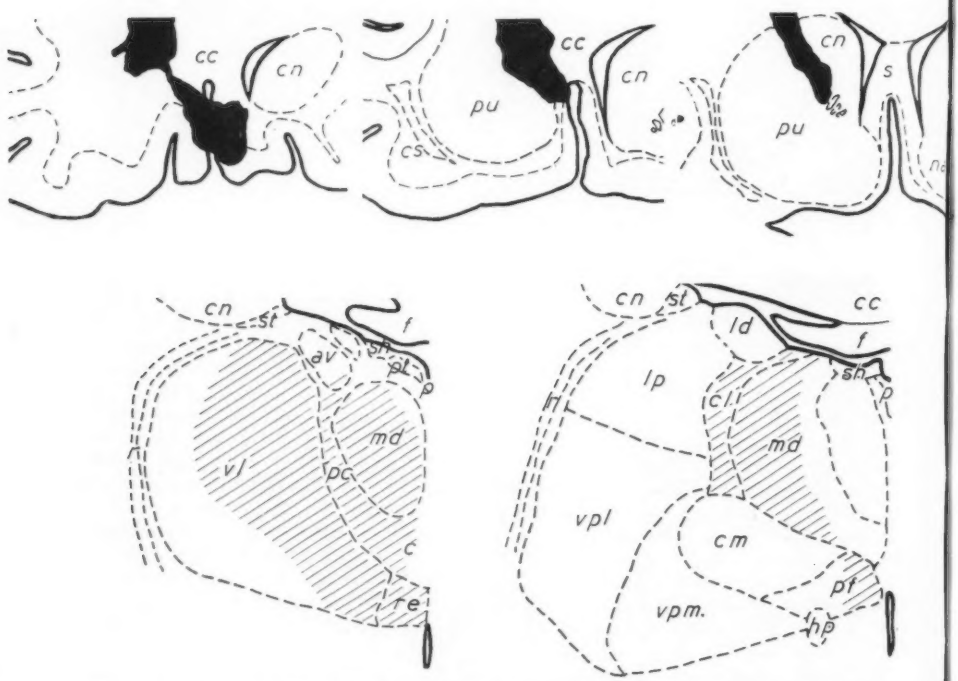


TEXT-FIG. 5.—The lesions and thalamic degeneration in monkey MI. 3. The right hemisphere is described as Experiment 8 and the left as Experiment 5.

the cross-sectional area of the nucleus is involved. Posteriorly, however, only the dorso-medial margin abutting on the parafascicular nucleus is affected. In the parafascicular nucleus itself cell loss and gliosis can be seen in the lateral part of the nucleus where it merges with the centromedian. The degeneration is more marked caudally, but that part of the nucleus medial to the habenulo-peduncular tract is intact. The midline nuclei, reuniens, paratænialis, and the paraventricular nuclei, do not show any sign of degeneration. The rostral end of the reticular nucleus, together with the underlying lateral part of the nucleus ventralis anterior, show characteristic degenerative changes. The other main nuclei affected are the lateral margin of the mediodorsal nucleus, and the ventro-medial parts of the nuclei ventralis lateralis and ventralis posterior.

Experiment 5 (MI.3L).—Post-operative survival ten weeks.

In addition to destroying most of the anterior cingulate area, the lesion has involved the dorso-lateral corner of the head of the caudate nucleus from just behind its rostral end back almost to the level of the septum. It also extends across the dorsal third of the internal capsule to involve the putamen. In its rostral moiety the dorsal half to two-thirds of the putamen is destroyed, but caudally the damage is restricted to a narrow cut through the middle third of its vertical extent (text-fig. 5).



TEXT-FIG. 6.—Diagram illustrating the striatal damage and retrograde degeneration in Experiment 6.

The thalamic nuclei centralis medialis, paracentralis and centralis lateralis show almost total retrograde cell degeneration in their rostral parts as indicated by the marked cell loss and gliosis which has occurred. In all of these elements, however, an increasing number of normal cells is found as their caudal limits are approached. In the parafascicular nucleus the dorso-lateral two-thirds show complete cell atrophy anteriorly, but further caudally the degeneration becomes progressively restricted, first to the dorsal half and then to the dorso-lateral quadrant of the nucleus at its caudal end. The immediately adjoining portion of the centromedian nucleus shows similar changes, but the bulk of the nucleus is unaffected. The nucleus ventralis anterior, together with the overlying reticular nucleus, are almost completely degenerated, as are the anteromedial, the medial part of the anteroventral, and the mediodorsal nucleus.

Experiment 6 (MI.10).—Post-operative survival fourteen weeks.

After complete destruction of the rostral half of the head of the caudate nucleus and the adjacent parts of the internal capsule and putamen, severe retrograde degeneration has occurred in the nuclei centralis medialis, paracentralis, centralis lateralis and parafascicularis (text-fig. 6).

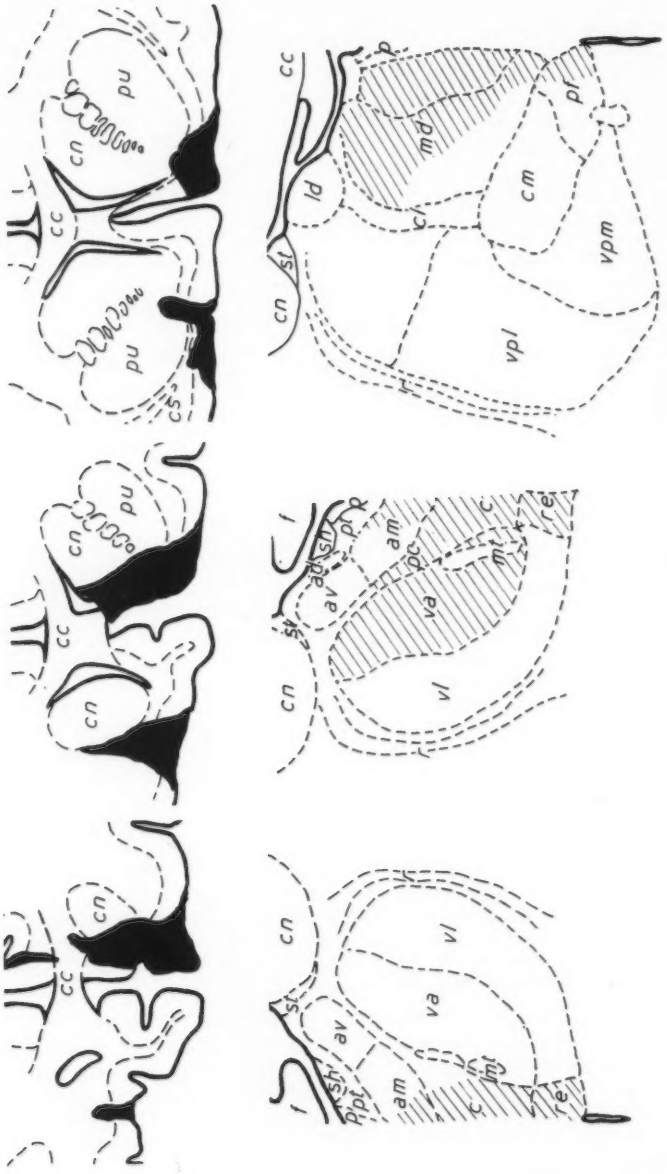
Extending from just in front of the genu of the corpus callosum back to the level of the rostral end of the septum the cortex of the infero-medial aspect of the hemisphere has been ablated as well as the overlying anterior cingulate area. The rostral half of the head of the caudate nucleus is completely destroyed, but the damage ends abruptly opposite the anterior end of the septum. Throughout this extent, and for a short distance behind the lesion in the caudate nucleus, the internal capsule and the dorso-medial aspect of the putamen have also been involved. The medial surface of the rostral end of the nucleus accumbens may also have been damaged by the ventral extension of the lesion.

In the thalamus the nucleus centralis lateralis has completely disappeared back to the level of the middle of the centromedian nucleus. Behind this level a number of cells reappear in the ventral, vertical part of the nucleus, but its dorsal part (above the medio-dorsal nucleus) is still devoid of cells. The paracentral nucleus is likewise totally degenerated throughout its entire rostro-caudal extent. The lateral part of the nucleus centralis medialis is severely affected, but adjacent to the midline a large number of shrunken cells remain. In the parafascicular nucleus there is obvious evidence of cell loss and gliosis, especially in its medial part. In the lateral part of the nucleus, where it adjoins the centromedian, isolated patches of gliosis and cell shrinkage occur. In the centromedian nucleus there is no sign of cell atrophy, but in its rostral third there is a diffuse gliosis, no doubt due to degeneration of fibres of passage from the parafascicular nucleus. The nucleus reuniens is atrophied throughout its entire antero-posterior extent. The nuclei ventralis anterior and reticularis are both severely degenerated in their rostral parts. Of the principal nuclei the anteromedial, anterodorsal, medial part of the anteroventral, the lateral two-thirds of the mediodorsal and most of the nucleus ventralis lateralis all show marked cell loss.

Experiment 7 (MI.9L).—Post-operative survival fourteen weeks.

The lesion appears at the level of the anterior tip of the lateral ventricle, destroying at this level only a small area of the orbital cortex. At slightly more caudal levels it reaches dorsally to involve the lateral margin of the head of the caudate nucleus, the lower half of the internal capsule and the medial margin of the putamen. It does not extend beyond the level at which the septal nuclei first appear.

The nucleus reuniens is completely degenerated together with the nucleus centralis medialis. Rostrally the nucleus paracentralis is severely affected with



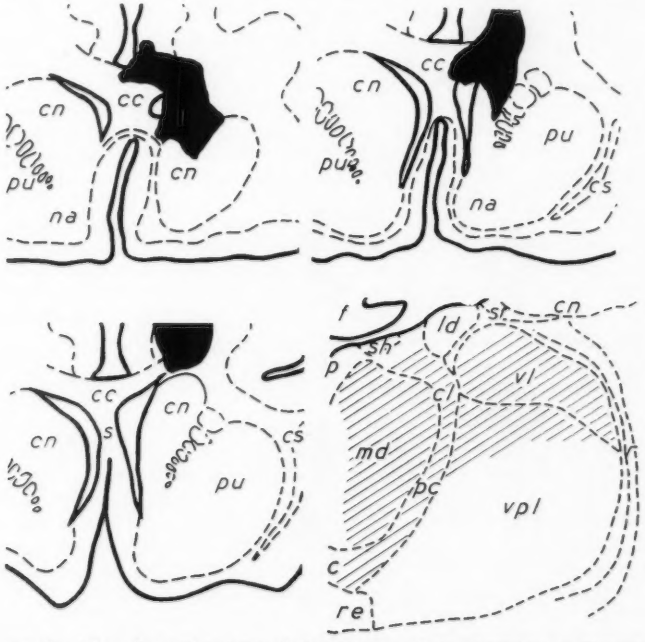
TEXT-FIG. 7.—The lesions and degeneration in Experiments 7 and 11.

the exception of a few shrunken cells at its ventro-lateral margin. Further caudally, a number of normal cells are found in its lateral part, where it abuts on the nucleus centralis lateralis, which is unaffected. While the centromedian nucleus shows no change, there is some evidence of retrograde degeneration in the medial part of the parafascicular nucleus, especially at its rostral end. The only main nuclei which are affected are the mediodorsal, the ventralis anterior and the antero-medial nuclei. Of these, the medio-dorsal is almost completely degenerated (including its medial magnocellular portion), while the medial part of the antero-medial and the large-celled part of the ventralis anterior show severe cell loss and gliosis (text-fig. 7).

Experiment 8 (MI.3R).—Post-operative survival ten weeks.

The aspirator in this experiment penetrated the medial aspect of the hemisphere, below the corpus callosum, from the opposite side. The narrow track of the lesion extends through the rostral part of the septum; passing through the junctional zone between the caudate nucleus and the nucleus accumbens it reaches across the inferior end of the internal capsule to the ventro-medial corner of the putamen. The main portion of the lesion lies rostral to this level, and involves principally the ventro-medial angle of the caudate head—almost to its rostral end. The ventral extent of the lesion has also undercut the posterior orbital cortex (text-fig. 5).

The thalamic degeneration is relatively localized. In the nucleus centralis medialis there is a complete cell loss and gliosis anteriorly, but in its posterior half the lateral part of the nucleus is virtually normal. The adjoining nucleus paracentralis is quite intact, as is also the nucleus centralis lateralis. There



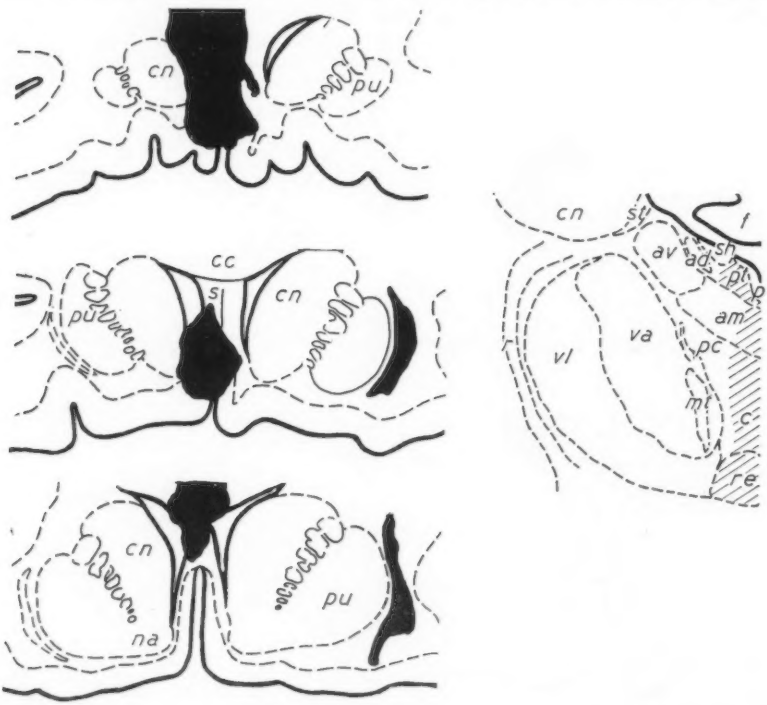
TEXT-FIG. 8.—The site and extent of the lesion and degeneration in Experiment 9.

is some evidence of cell shrinkage in the rostral part of the paratænial nucleus, but there is no definite cell loss or gliosis in this element. Although for the most part the centromedian nucleus is quite normal, there may be some degeneration at its rostral end, especially in the ventral half. The only principal nucleus which is involved is the mediodorsal, in which the magnocellular part is severely degenerated.

Experiment 9 (MI.12).—Post-operative survival nine weeks.

In this experiment the lesion, in addition to undercutting the anterior cingulate cortex, destroys the dorsal half to two-thirds of the rostral and of the head of the caudate nucleus back to just in front of the septum. The dorsal half of the internal capsule is encroached upon, and for a very short distance anteriorly the dorsal margin of the putamen has also been involved (text-fig. 8).

The nucleus centralis medialis is totally degenerated rostrally, but many shrunken cells persist in its caudal part. In the nucleus paracentralis only a few normal cells remain along the ventral border of the oral end of the nucleus; the number of normal cells becomes progressively more numerous towards the posterior end of the nucleus. Anteriorly, there is a good deal of degeneration in the nucleus centralis lateralis, but opposite the centromedian nucleus it is intact, except for its most dorsal part. The parafascicular nucleus shows some cell shrinkage and



TEXT-FIG. 9.—Monkey MI. 5. The lesions of Experiments 10 and 15 and the thalamic degeneration in Experiment 15.

gliosis in its dorso-medial quadrant, but the rest of this nucleus and the centromedian are quite normal.

Of the principal nuclei a varying degree of degeneration is found in the anterior group, the mediodorsal nucleus, the dorsal half of the nucleus ventralis lateralis, and the nucleus ventralis anterior.

Experiment 10 (MI.5R).—Post-operative survival eleven weeks.

To eliminate the possibility that the fibres of the centromedian and the parafascicular nuclei project, through the putamen, to either the claustrum, the insula or the cortex of the orbito-insular junction a control experiment was done in this monkey.

A narrow electrolytic lesion was placed in the white matter immediately lateral to the putamen from just behind its rostral end to the level of the interventricular foramen. The entire rostral part of the claustrum and external capsule have been destroyed, together with the white matter ventro-lateral to the putamen. Throughout this extent the orbito-insular cortex has been isolated from the putamen. The latter structure, however, is quite intact. The only detectable degeneration in the thalamus is a small area of cell loss and gliosis in the nucleus ventralis lateralis due to the electrode track in the upper part of the internal capsule (text-fig. 9).

That the three intralaminar nuclei, centralis medialis, paracentralis, and centralis lateralis project to the head of the caudate nucleus in a similarly precise manner will be shown in the succeeding group of five experiments. An important finding, which will be indicated, is that degeneration in these nuclei can occur without involvement of the internal capsule, and independently of the principal thalamic nuclei.

Experiment 11 (MI.9R).—Post-operative survival fourteen weeks.

The principal damage in this hemisphere is to the cortex of the medial surface of the hemisphere in front of and ventral to the corpus callosum, and to the ventromedial part of the head of the caudate nucleus. The medial neocortex is completely destroyed from just behind the rostral pole of the hemisphere to the anterior end of the septum. Above the corpus callosum the cingulate gyrus is only slightly involved. The ventro-medial half of the rostral end of the head of the caudate nucleus has been ablated, but posteriorly this damage becomes more restricted so that the caudate is completely spared before the septum is reached. The rostral part of the nucleus accumbens is partially damaged, together with the adjacent ventral part of the internal capsule.

In the thalamus the nuclei reuniens and centralis medialis are totally degenerated while the paratænial nucleus shows evidence of cell loss and shrinkage in its rostral part. Of the principal nuclei, only the anteromedial is affected (text-fig. 7).

Experiment 12 (MI.7L).—Post-operative survival fifteen weeks.

After a lesion in the anterior and medial parts of the head of the caudate nucleus degeneration is confined to the medial elements of the intralaminar group and the nuclei of the midline.

The track of the lesion in this monkey extends forwards and ventrally through the centrum ovale to involve most of the orbital and medial neocortex back to the level of the caudate head. The extreme rostral end of the head of the caudate nucleus is completely destroyed, but posteriorly the extent of this damage rapidly diminishes and becomes restricted to its medial margin. This part of the lesion, although small in cross-sectional area, also involves the adjacent part of the lateral septal nucleus back to the level of the interventricular foramen.

The nucleus reuniens is completely degenerated, as is also the rostral part of the nucleus centralis medialis. Further caudally, however, the dorsal part of the latter element is largely preserved. The medial part of the nucleus paracentralis is severely affected anteriorly, but the lateral and posterior portions of the nucleus are intact. There is no degeneration in any of the remaining midline and intralaminar nuclei. The magnocellular part of the mediodorsal nucleus and the nucleus ventralis anterior are the only principal nuclei involved.

Experiment 13 (MI.7R).—Post-operative survival fifteen weeks.

Degeneration confined principally to the nucleus centralis lateralis has occurred after a small lesion in the dorso-lateral part of the caudate nucleus and the adjacent part of the internal capsule.

The lesion, which is very restricted both in its medio-lateral and antero-posterior extent, only involves the dorso-lateral margin of the middle of the head of the caudate nucleus and the immediately adjacent white matter. Apart from the narrow electrode track the lesion does not exceed 2 mm. in any dimension.

The thalamic degeneration shows an equally marked localization, being confined to the nucleus centralis lateralis and the immediately adjacent part of the nucleus paracentralis. In both these nuclei there is a marked cell loss and gliosis which becomes progressively less severe posteriorly. The adjoining main nuclei, i.e. nucleus lateralis posterior, nucleus ventralis posterior and the mediodorsal nucleus, all show slight retrograde changes.

Experiment 14 (MI.6).—Post-operative survival ten weeks.

A small lesion of the medial aspect of the head of the caudate nucleus, without involvement of the internal capsule or putamen has resulted in degeneration restricted mainly to the nucleus centralis medialis and paracentralis.

The lesion extends through the cingulate gyrus from the level of the genu of the corpus callosum back to the rostral end of the septum. At the middle of its antero-posterior extent it passes through the ventricle to destroy the medial margin of the head of the caudate nucleus anteriorly and its dorso-medial half more caudally. The caudate involvement reaches from its rostral end back to the junction of its middle and anterior thirds.

Retrograde cell degeneration in the thalamus is found in the nucleus centralis medialis, the paracentralis, the ventralis anterior, the anterior nuclei and the mediodorsal nucleus. The nucleus centralis medialis is completely devoid of cells in its anterior part, but posteriorly only cell shrinkage is evident. In the nucleus paracentralis there is only a slight cell loss with some shrinkage of the persisting cells in its rostro-medial part.

Experiment 15 (MI.5L).—Post-operative survival eleven weeks.

Following a lesion confined to the medial part of the caudate head and the overlying neocortex degeneration has occurred in the nucleus centralis medialis, the nucleus reuniens and the nucleus paratænialis (text-fig. 9).

In serial sections through the lesion it is seen that the entire medial neocortex beneath the rostrum of the corpus callosum, from just in front of the genu back to the anterior end of the septum, has been destroyed or isolated. In addition to this, the medial surface of the extreme rostral end of the head of the caudate nucleus has been involved by the track of the electrode, but behind this only the overlying corpus callosum has been damaged. A small lateral extension of the lesion, however, has penetrated the nucleus accumbens just in front of the septum, but only for a short antero-posterior distance.

The medial half to two-thirds of the nucleus centralis medialis is severely degenerated at its anterior end. In successively caudal sections, however, the

medio-lateral extent of the degeneration becomes progressively more restricted until the level of the middle of the nucleus, behind which it is quite normal. In the nucleus reuniens there is a marked shrinkage and pallor of many of the cells and some slight cell loss throughout its antero-posterior extent. The paratænial nucleus in this experiment shows some evidence of cell loss, and all the persisting cells are shrunken and paler staining. Similar changes are seen in the medial part of the anteromedial nucleus. No other thalamic nuclei are affected.

The last two experiments have been included because together they delimit the projection of the nucleus reuniens to the cortex of the medial surface of the hemisphere below and in front of the corpus callosum.

Experiment 16 (MI.8).—Post-operative survival twelve weeks.

The lesion commences a few millimetres behind the rostral pole of the hemisphere where it has involved the ventralmost cortex of the medial surface. Traced posteriorly, the damage is seen to become progressively more dorsal in position, and for a short distance in front of the genu of the corpus callosum the dorsal two-thirds of the medial surface has been completely destroyed; owing to the extensive damage of the centrum ovale the remaining cortex has probably been isolated from the thalamus. The rostral tip of the head of the caudate nucleus has also been marginally involved, but the damage to this structure extends, at the most, for only half a millimetre caudally. Behind this level, the lesion is confined to the cortex and white matter above the caudate nucleus as far back as the level of the septum.

The nucleus reuniens is almost totally degenerated throughout its antero-posterior extent, only a few shrunken cells persisting in the ventro-medial part of its cross-sectional area. The adjacent part of the rostral extremity of the nucleus centralis medialis shows cell loss and gliosis, but the greater part of the nucleus is definitely intact. Apart from this, the only other degeneration is that found in the principal nuclei, including the anterior nuclei, ventralis anterior and ventralis lateralis. The severe degeneration in the nucleus ventralis anterior is particularly noteworthy, since it is out of all proportion to the slight striatal damage and indicates that almost certainly the projection of this nucleus is extra-striatal.

Experiment 17 (MI.12L).—Post-operative survival fourteen weeks.

The lesion in this hemisphere is confined to the cortex beneath the rostrum of the corpus callosum, reaching from just behind the genu to the rostral end of the septum. At no point does it encroach upon the striatum or even upon the white matter immediately beneath the cortex. The only degeneration seen in the thalamus of this side is a partial, diffuse cell loss in the nucleus reuniens. Although it is difficult to assess the severity of this degeneration in the absence of a "control side," it is not nearly as severe as that seen in Experiment 16 (MI.8). It is of interest that although the cortical ablation in this experiment included part of the area designated, area 24 (anterior cingulate) by Brodmann (1905) and Walker (1940), this part apparently receives no afferent fibres from the anteromedial nucleus, as this element shows no detectable cell loss or gliosis.

Discussion

Before discussing our findings in detail it is necessary to emphasize that, as far as can be judged, the process of retrograde degeneration in the midline and intralaminar nuclei is the same as in all other dorsal thalamic elements. In this respect these nuclei differ from the thalamic reticular

nucleus, a derivative of the ventral thalamus (Rose and Woolsey, 1949). As Rose (1952) has pointed out, degeneration in the reticular nucleus is characterized by a profound alteration of the cells rather than their disintegration; in general the topographical distribution of the changes in this element correspond to those in the principal nuclei in their distribution, but appear to occur at a slower rate. Chow (1952) has confirmed these findings in the macaque, and our own observations on the reticular nucleus are in essential agreement with his. On the other hand, in the midline and intralaminar nuclei, degeneration is of the classical "retrograde" type, in that nearly all cells disappear at the same rate as those in the main nuclei, and individual elements of the group may degenerate both completely and independently of the principal nuclei. Thus, whereas the changes in the reticular nucleus may possibly be interpreted as being "transneuronal" in nature, all the available evidence indicates that the degeneration of the cells of the midline and intralaminar nuclei is the direct result of interruption of their axons. Since this degeneration occurs after the extrathalamic lesions (Nissl, 1913; Rose and Woolsey, 1943; Stefens and Droogleever Fortuyn, 1953; Powell and Cowan, 1954; Cowan and Powell, 1955) it must be concluded that the axons of these cells pass beyond the confines of the thalamus (*cf.* Hanbery, Ajmone-Marsan and Dilworth, 1954), and collaterals to the reticular or other thalamic nuclei (if these do indeed exist) probably play a minor role, since they are not capable of maintaining the integrity of the cell after severance of its main axon (*cf.* Starzl and Magoun, 1951).

The two significant findings which have emerged from this study are: (*a*) the presence of a more extensive thalamo-striatal projection than has hitherto been demonstrated, and (*b*) the presence of a precise topical organization within this thalamo-striate system.

To facilitate discussion, the projection of individual nuclei will now be considered.

The Centromedian Nucleus

The hemi-decortication experiments of Walker (1935, 1938a) clearly established that the centromedian nucleus does not project directly to any part of the cerebral cortex. In one of his cases, however, in which most of the caudate nucleus, globus pallidus, and all of the putamen were involved, the centromedian nucleus was found to be severely degenerated (Walker 1938b). Because only slight degeneration had been found in this nucleus in other experiments in which the striatum was encroached upon, he was led to suggest that the centromedian nucleus might be related to the globus pallidus—although, as he himself pointed out, this lacked phylogenetic significance, the centromedian nucleus being more recent than the globus pallidus. Mettler, in his earlier papers (1943, 1945) expressed the same opinion, but on reconsidering the problem in 1947 he felt less certain about

the exclusion of the striatum, and in a further experiment (his case J.171) he specifically states that after destruction of the centromedian nucleus, fine Marchi degeneration was found in the putamen, but none could be traced into the pallidum. On the basis of human pathological material, C. and O. Vogt (1941) Freeman and Watts (1947) and McLardy (1948), all conclude that this nucleus projects to the striatum (putamen + caudate), each presenting a case for excluding its projection to the globus pallidus. Essentially similar conclusions have been arrived at by Hassler (1948) and Simma (1951). Recently Nauta (1954), using a modified Bielchowsky technique has described degenerating fibres which pass from this nucleus to terminate in the adjacent thalamic nuclei, the putamen, globus pallidus and claustrum.

In the present series of experiments six hemispheres with varying amounts of degeneration in the centromedian nucleus have been described. In view of the obvious significance of this element in the Primate thalamus and because of the uncertainty which exists concerning its projection, this material will be discussed in some detail. The common feature in all these experiments is that in each case the putamen has been involved to a greater or lesser extent. Although in many of the experiments the lesion had also encroached upon the caudate nucleus there are a number of cases in which destruction of the caudate, without involvement of the putamen, resulted in no change in this nucleus. Furthermore, in the majority of cases in which degeneration has occurred in the centromedian nucleus, the globus pallidus has escaped involvement. That the afferent fibres of the nucleus are not merely passing through the nucleus *en route* to the claustrum or insular cortex is apparent from Experiment 10, in which again no degeneration was found in the nucleus, although the lesion in this case almost completely isolated these structures. From these considerations, and from a critical reappraisal of the literature, it is clear that the centromedian nucleus projects exclusively to the putamen.

Since the severity and extent of the degeneration in the nucleus varied in many of the experiments a correlation of this with the site of the lesion has enabled us to work out the details of its projection. When the posterior half of the putamen is isolated, as in Experiment 3, the retrograde cell degeneration is confined to the posterior part of the centromedian nucleus. Experiment 2 is complementary to this in that approximately the anterior half of the nucleus has degenerated after destruction of the rostral half of the putamen. When the dorso-medial portion of the putamen was involved (as in Experiment 4) cell degeneration was most marked in the dorso-medial part of the nucleus. From these experiments and from other experiments with smaller lesions, it is apparent that the projection of the nucleus is organized both antero-posteriorly and medio-laterally.

This conclusion is not at variance with the observations of other workers, as a careful examination of their descriptions will show. Three further

examples may be cited from the literature. The first is that of Le Gros Clark and Russell (1939) who described a human case with a lesion in the external capsule and posterior part of the putamen which isolated the insular cortex; neither the caudate nucleus nor the globus pallidus were involved. Apart from a few cells at its medial extremity the centromedian nucleus was totally degenerated. These authors were also able to show experimentally that, in the macaque at least, the centromedian nucleus does not project to the insular cortex, but in view of the conflicting evidence at that time the question was left unsettled. In a recent human case of hemi-decortication (Powell, 1952) in which the lateral aspect of the putamen was involved, cell loss was found throughout the ventro-lateral part of the centromedian nucleus. The third example is that of Pribram and Bagshaw (1953); although a detailed description of their anatomical findings is not given, it appears from their diagrams that the only two experiments in which degeneration had occurred in the centromedian nucleus (FT. 3 and I 1) are just those cases in which, as they state, the putamen was involved. In summary, it may be said that in all cases in the literature available to us in which degeneration has been described in the centromedian nucleus there has been unequivocal involvement of the putamen; usual concomitant damage of the caudate nucleus, however, accounts for the commonly accepted conclusion that this nucleus projects to the corpus striatum (caudate + putamen). The increase in relative size which the centromedian nucleus undergoes in the Primate brain (Le Gros Clark, 1932) may be correlated with a similar increase in the relative size of the putamen. Harman and Carpenter (1950) have shown in a graded series of Primate brains that "the relatively large caudate nucleus of prosimians decreases as the Primate scale is ascended and there is a corresponding increase in the volume of the putamen."

The Nucleus Parafascicularis

Our previous observation in the rabbit (Cowan and Powell, 1955) that the parafascicular nucleus also projects to the putamen has been confirmed and extended in the present study. In both species it has been found that this nucleus shows no change even after extensive involvement of the caudate nucleus. Experiment 3 of this series clearly shows that, at least in the monkey, this nucleus does not project to the caudal part of the putamen. Smaller overlapping lesions (e.g. Experiments 6 and 7) restricted to the rostro-medial part of the putamen, indicate that this is the projection field of this thalamic element, and also show that there is some degree of organization within its projection. The complete preservation of the nucleus in the human case already alluded to (Le Gros Clark and Russell 1939) where the rostral part of the putamen was preserved, provides further confirmation of this finding. These conclusions are not in complete agreement with those of Gerebtzoff (1940), who, in the rabbit, has described

chromatolysis in the cells of this nucleus after lesions restricted to the caudate nucleus as well as after lesions in the putamen; on this evidence Droogleever Fortuyn (1953) has claimed that the centromedian nucleus projects only to the putamen despite Gerebtzoff's concluding statement: "en conclusion, les fibres thalamo-striées sont issues des noyaux antero-interne, ventral interne et parafasciculaire et gagnent le striatum (noyau caudé et putamen)."

Since the degeneration of the parafascicular nucleus has frequently occurred in these experiments without involvement of the nucleus accumbens, Simma's (1951) deduction that the parafascicular nucleus projects to the fundus striati (= nucleus accumbens) has not been confirmed.

The Intralaminar Nuclei-Centralis Medialis, Paracentralis, and Centralis Lateralis

As a group, these nuclei have received less attention anatomically than the centromedian and parafascicular nuclei, possibly on account of their apparent regression in ascending phylogeny, and the associated difficulty of clearly differentiating them from the adjacent principal nuclei. Recent experimental work (Stefens and Droogleever-Fortuyn, 1953; Powell and Cowan, 1954; Cowan and Powell, 1955) however, has established that in lower forms (rat and rabbit) these nuclei are directly connected with the head of the caudate nucleus. The present study has shown that this relationship holds true in the Primate brain and has confirmed and extended the finding of a topical organization within this projection, as suggested by our previous work.

Large lesions in the head of the caudate nucleus (with or without the involvement of the putamen) consistently result in retrograde degeneration in this group of nuclei (for example, Experiments 2 and 9). Localized, overlapping lesions in the caudate result in a varying degree of degeneration of individual elements of the group, and in some cases, within an individual nucleus. In Experiments 14 and 15, for example, only the rostro-medial margin of the caudate head was destroyed, and the resulting thalamic degeneration was confined to the rostral part of the nucleus centralis medialis. Degeneration in the more lateral elements of the group (centralis lateralis and paracentralis) only resulted when the lateral part of the caudate nucleus was encroached upon (e.g. Experiments 5 and 7). Similarly, when only the most rostral tip of the caudate head was involved, degeneration was restricted to the rostral part of the associated nuclei (for example, Experiment 11) and for degeneration to occur further caudally in these nuclei, damage to the posterior part of the head of the caudate was necessary, as in some of the larger lesions (for example, Experiment 2). After collating all the relevant experiments, it is clear that within this group there is a medio-lateral and antero-posterior organization similar to that demonstrated for the centromedian nucleus.

Although Walker (1938b) did not determine the projection of these nuclei, a re-examination of the material which he described is in full accord with our findings. An example which might be quoted is his Case 1 (1935) in which the excision had involved the lateral portion of the head of the caudate nucleus. In the description of the relevant nuclei, he states: ". . . the nucleus centralis medialis . . . is quite normal in appearance" and "the nuclei paracentralis and centralis lateralis are readily recognized, but appear to be composed of fewer, although normal cells."

Pribram and Bagshaw (1953) conclude that at least the medial intralaminar nuclei project to the posterior orbital gyrus and anterior perforated substance, but it is doubtful whether their conclusion is justifiable, since in the relevant experiments the caudate nucleus was always involved. (*See* their figs. 6 and 7.)

Nashold, Hanbery and Olszewski (1954) claim that lesions confined to the neocortex will result in "marked changes" in the intralaminar nuclei, and that lesions "restricted to the caudate and putamen did not result in degeneration in the thalamic nuclei." Degeneration in the "oral part of the intralaminar nuclei" was, however, found when lesions of the caudate nucleus also involved adjacent portions of the internal capsule. Regarding the first of these observations, it can only be said that the weight of evidence (*see* Walker, 1938b) is against this view, and we ourselves have never observed retrograde cell changes in these nuclei after cortical lesions. Although we have no experiment in which the lesion is strictly confined to the basal ganglia, in Experiment 14 unequivocal degeneration was found in the nucleus centralis medialis, following a lesion in the caudate nucleus, which at no point encroached upon the internal capsule itself. We also have a case (MI. 13R) which although not meriting a detailed description might be mentioned in this connection. In this hemisphere a large lesion was placed in the cortex and subcortical white matter immediately dorsal to (but not involving) the caudate nucleus and putamen. Although the relevant principal nuclei showed severe retrograde degeneration, no change was seen in any of the mid-line or intralaminar nuclei. Should it be postulated that the projection to the caudate nucleus is by way of collaterals, the fact that these nuclei appear to degenerate only after involvement of this structure suggests, at least, that this is the major functional connection. A fuller consideration of the findings of these authors is not, at present, possible, as their results have so far been given only in abstract.

The technical difficulties inherent in the use of silver techniques, and particularly after thalamic lesions, in which fibres of passage could be damaged, should be borne in mind in interpreting the findings of Nauta (1954). In his study, fibres were traced from the nuclei centralis lateralis and paracentralis to other thalamic nuclei, to the caudate, putamen, claustrum, and to the infralimbic and cingulate areas. Some of this degeneration, as Nauta himself points out, is probably due to involvement of adjoining

nuclei, or of fibres passing through the nucleus centralis lateralis. For example, it is known that no retrograde degeneration occurs in the intralaminar nuclei after lesions of the cingulate, or infralimbic areas (Rose and Woolsey, 1948; Cowan and Powell, 1955). Regarding the connections with the caudate, however, he states that "there appears to be somewhat better evidence of a projection from the nucleus centralis lateralis."

In a human pathological case described by one of us (Powell, 1952) gliosis was described in the intralaminar nuclei after a lesion destroying at least the anterior 5 mm. of the striatum. Although at the time this was interpreted as being due to degeneration of fibres of passage, it is almost certain that this represented a partial retrograde cell degeneration.

Paratænial Nucleus

The exact projection of this nucleus is still uncertain. Stoffels (1939a and b), Lashley (1941) and Droogleever-Fortuyn (1950) have suggested that it projects to the cortex on the medial surface of the hemisphere immediately rostral to the septum (i.e. the retrobulbar area or the tænia tecta). In our previous study, however (Cowan and Powell, 1955), complete destruction of the cortex on the medial surface of the hemisphere, back to, and including the septum, but without involvement of other subcortical structures, never resulted in degeneration in this element. In that paper it was tentatively concluded that the paratænial nucleus is related to the nucleus accumbens, but as a lesion confined to this structure has not yet been obtained, this problem remains unsettled. The present material, as far as it goes, is in accord with this view, since in the four experiments (1, 8, 10 and 14) in which degeneration was found in the paratænial nucleus, the nucleus accumbens had been involved. It was completely degenerated in the large lesion (Experiment 1) and only slightly affected in other experiments, in which the nucleus accumbens was only marginally damaged. This thalamic nucleus showed no change, when the medial surface alone was damaged (Experiments 15 and 16) or after large caudate or putamen lesions (Experiments 2 and 3).

Nucleus Reuniens

It is now established that in lower mammals the nucleus reuniens projects directly to the cortex of the infralimbic area (Rose and Woolsey, 1948; Droogleever-Fortuyn, 1950; Cowan and Powell, 1955). That a similar relationship holds true for the monkey is borne out by the present study. Although our evidence on this point is not critical, a comparison of Experiments 15 and 16 indicates that it projects to the area designated by Walker (1940) as area 25.

Paraventricular Nuclei

It is of interest that in Experiment 1 the anterior and posterior paraventricular nuclei have degenerated. The only other descriptions of degeneration in these nuclei are the single experiment of Walker (1936) and

our previous observations (Powell and Cowan, 1954; Cowan and Powell, 1955). Although we have never had a lesion resulting in selective degeneration in the paraventricular nuclei, a common feature of all the experiments appears to be the involvement of the lateral preoptic area. The most localized lesion which caused degeneration in these nuclei was in R29 of the rat material; here the preoptic and anterior hypothalamic areas were involved, together with the lower part of the internal capsule. That the hypothalamic damage in this experiment was not critical, however, is clear from rabbits 2 and 15 (Cowan and Powell, 1955) in which these nuclei had degenerated without involvement of this area. Further, the medial preoptic area may be excluded, since it was damaged, together with the anterior hypothalamic area in rabbit 45 without causing any cellular change in these nuclei, and by the first experiment of the present series, where this area had not been encroached upon. Lastly, structures anterior to the preoptic areas may be excluded, as degeneration has never been found after such rostral lesions. The possibility that these fibres merely traverse this area to end elsewhere cannot, of course, be excluded.

The Striatum and the Diffuse Thalamo-cortical Projection System

In 1942 Morison and Dempsey discovered that low-frequency stimulation of the midline and intralaminar nuclei results in widely distributed, high voltage cortical waves characterized by their long latency and an initial voltage increment. The similarity of these "recruiting responses" to the spontaneous spindle bursts recorded from the cortex of animals under barbiturate anæsthesia was emphasized and it was concluded that the two phenomena share a common (but undefined) neural path. Three alternative pathways by which these responses could be mediated were suggested: (*a*) that these nuclei may send axons directly to the cortex, (*b*) that the responses were mediated by way of the adjacent principal thalamic nuclei, or (*c*) that they were mediated by way of some separate neuronal system. Evidence has been adduced in support of each of these hypotheses; this will now be reviewed with particular reference to the present anatomical findings.

With the exception of the nucleus reuniens and the anterior nuclei (which have also been implicated in the so-called thalamic reticular system —Jasper, 1949 and Starzl and Magoun, 1951) the weight of experimental evidence, as we have shown, is against the hypothesis that this system is directly connected with the cerebral cortex. It should be mentioned, however, that in support of this view, Morison and Dempsey (1942) have quoted a personal communication from Lorente de No to the effect that the "non-specific cortical afferents" which he has described (1943) may subserve this response.

Other exceptions are the thalamic reticular nucleus and the nucleus ventralis anterior. As has been shown above, degeneration in the former

after cortical lesions cannot be taken as conclusive evidence that this nucleus projects directly to the cortex because of the difficulties in interpreting the peculiar features of this degeneration. The exact projection of the nucleus ventralis anterior has not been determined but there is evidence that its projection field is extrastriatal (*cf.* McLardy, 1950 and Experiment 16 of the present series). On the other hand the fact that recruiting responses may be recorded within this nucleus (Starzl and Magoun 1951), and from the cerebral cortex on stimulating the nucleus (Hanbery and Jasper, 1953; Hanbery, Ajmone-Marsan and Dilworth, 1954) is again not conclusive evidence that the constituent cells of this element (which probably project directly to the cortex) are implicated in the diffuse projection system, since it has been shown that the efferent fibres from the intralaminar nuclei traverse this nucleus (Powell and Cowan 1954). Involvement of these fibres may well account for the electro-physiological findings, and for the observation that destruction of the nucleus abolishes the recruiting responses (Hanbery and Jasper 1953) and also results in retrograde degeneration of the cells of the intralaminar nuclei (Powell and Cowan 1954).

The second possibility considered by Morison and Dempsey (1942) that the intralaminar nuclei form an intrathalamic diffusion system, was favoured by McLardy (1951) from a consideration of the anatomical evidence then available. Starzl and Whitlock (1952) were led to a similar conclusion. As they were able to record typical recruiting responses from the adjacent association nuclei of the thalamus on stimulating the intralaminar group, and only from the association areas of the cortex, they postulated that the responses were mediated by way of these nuclei. On the other hand, it has been shown that typical recruiting responses can be recorded from the cortex after destruction of the corresponding thalamic nucleus (Hanbery and Jasper, 1953). Another intrathalamic relay which has been postulated is by way of the nucleus ventralis anterior and the reticular nucleus (Hanbery, Ajmone-Marsan and Dilworth, 1954). As it is now clear that the midline and intralaminar nuclei will degenerate completely and independently of the principal nuclei, such a relay must be by way of collaterals for which there is, at present, no direct anatomical evidence.

The last possibility to be considered is that the diffuse response is mediated by way of other subcortical structures. It was originally suggested by Rose and Woolsey (1943, 1949) that the rostral part of the so-called "rhinencephalon" might be responsible; this conclusion was based upon their own experimental material and from a consideration of comparative anatomical studies. Against this view, however, are the findings of Starzl and Magoun (1951) that recruiting responses cannot be recorded from these rhinencephalic structures, and the anatomical evidence that degeneration does not occur in the midline and intralaminar nuclei after lesions restricted to the "rhinencephalon" (Powell and Cowan, 1954). On the

other hand the anatomical demonstration that most of the midline and intralaminar nuclei are directly related to the striatum makes it clear that this structure must, in some way, be implicated in the diffuse cortical projection. That this suggestion is not at variance with most of the physiological observations is apparent. For example, Starzl and Magoun (1951) have recorded responses from the caudate nucleus on stimulating the intralaminar system, Jasper (1954) indicates in his illustrations that stimulation of the caudate nucleus gives rise to typical recruiting responses in the cortex (his figure 5A); essentially similar results have been obtained by Stoupel and Terzuolo (1954) both on stimulating and recording from the caudate nucleus.

In spite of these observations, Ajmone-Marsan and Dilworth (1953) are of the opinion that the striatum plays only a minor role as a relay in the diffuse projection system, since they state that: "more or less extensive lesions in the caudate nucleus only slightly affect the cortical recruiting response, but do not abolish it."

SUMMARY

(1) The retrograde cell degeneration in the thalamus following lesions in the corpus striatum has been studied in the monkey.

(2) The centromedian and parafasicular nuclei have been shown to project to the putamen only; within the projection there is a precise topical organization.

(3) The intralaminar nuclei, centralis medialis, paracentralis and centralis lateralis project to the head of the caudate nucleus in a similarly organized manner.

(4) The nucleus reuniens is directly related to the cortex of the infralimbic area (area 25); the paratænial nucleus probably projects to the nucleus accumbens and the paraventricular nuclei appear to be related to the lateral pre-optic area.

(5) These findings have been discussed in relation to the anatomical literature and to the physiological concept of a diffuse thalamo-cortical projection system.

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ABBREVIATIONS

a c	anterior commissure	o c	optic chiasma
a d	anterodorsal nucleus	o t	optic tract
a h	anterior hypothalamic area	p	paraventricular nuclei
a m	anteromedial nucleus	p a	globus pallidus
a v	anteroventral nucleus	p c	nucleus paracentralis
c	nucleus centralis medialis	p f	parafascicular nucleus
c c	corpus callosum	p t	paratænial nucleus
c l	nucleus centralis lateralis	p u	putamen
c m	centromedian nucleus	r	reticular nucleus of thalamus
c n	caudate nucleus	r e	nucleus reuniens
c p	cerebral peduncle	s	septum
c s	claustrum	s h	stria habenularis
f	fornix	s n	subthalamic nucleus
h	hypothalamus	s o	supra-optic nucleus
h p	habenulo-peduncular tract	s t	stria terminalis
i c	internal capsule	t h	thalamus
l d	nucleus lateralis dorsalis	v a	nucleus ventralis anterior
l g	lateral geniculate nucleus	v l	nucleus ventralis lateralis
l p	nucleus lateralis posterior	v p l	nucleus ventralis posterior lateralis
m d	mediodorsal nucleus	v p m	nucleus ventralis posterior medialis
m p a	medial pre-optic area		
m t	mamillo-thalamic tract		
n a	nucleus accumbens		

LEGENDS FOR PLATES

PLATE XXXII

FIG. 1.—To show the retrograde cell degeneration in the nucleus centralis lateralis in Experiment 4 (MI. 13L). This and the subsequent photomicrographs are of thionine-stained sections at a magnification of × 37.

FIG. 2.—Degeneration in the medial part of the centromedian nucleus in Experiment 3 (MI. 11). The area of degeneration is delimited by the dotted line.

PLATE XXXIII

FIG. 3.—Localized degeneration in the medial part of the nucleus centralis medialis in Experiment 6 (MI. 8).

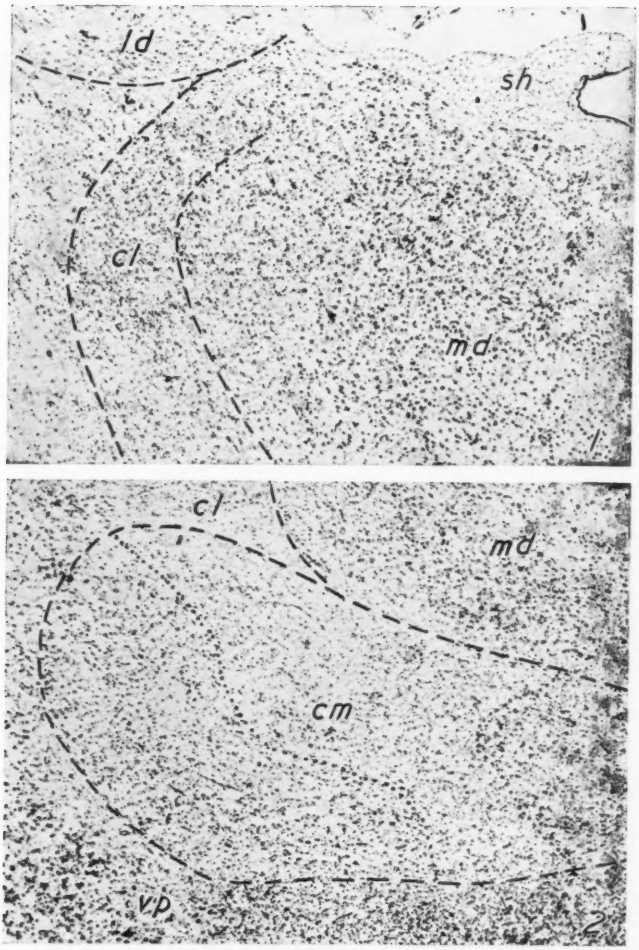
FIG. 4.—Degeneration confined to the medial part of the parafascicular nucleus in Experiment 6 (MI. 10).

PLATE XXXIV

FIG. 5.—To show the severity of the degeneration in the anterior paraventricular, paratænial and central medial nuclei in Experiment 1 (MI. 4). The arrows indicate the midline.

FIG. 6.—Degeneration in the nucleus paracentralis in Experiment 4 (MI. 13L).

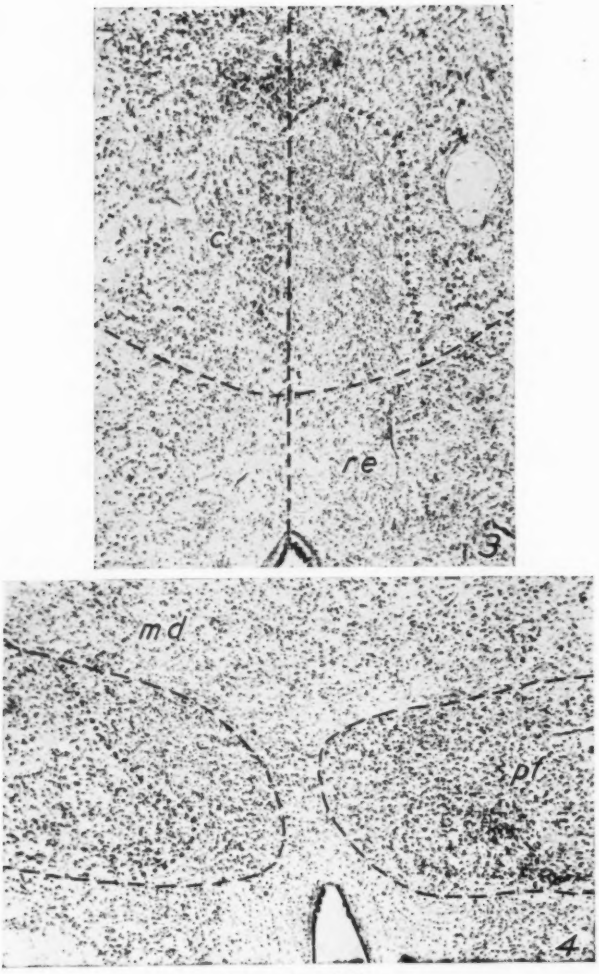
PLATE XXXII



FIGS. 1 and 2.

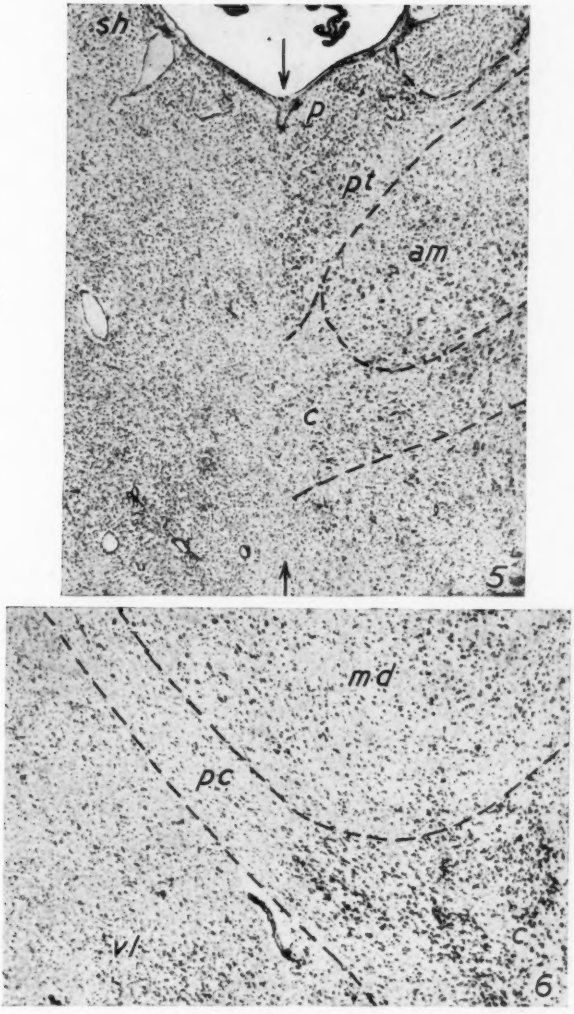
To illustrate article by T. P. S. Powell and W. M. Cowan.

PLATE XXXIII



FIGS. 3 and 4.

To illustrate article by T. P. S. Powell and W. M. Cowan.



FIGS. 5 and 6.

To illustrate article by T. P. S. Powell and W. M. Cowan.

NOTICES OF RECENT PUBLICATIONS

EPILEPSY

Krampfbereitschaft. By GERHARD KOCH. 1955. Pp. xii + 252. Illustrations 45. Tables 17 and pedigrees 27. Rome: Edizioni dell' Isituto Gregorio Mendel. Price 5,000 L.

The first section of this book provides a comprehensive critical review of past work on epilepsy, especially on its pathogenesis and constitutional and hereditary aspects. The author accepts the view, which is becoming the prevalent one, that in the generality of epilepsies no single major gene plays the predominant role in ætiology. Genetic factors are probably multiple, and the constitutional predisposition is regarded as quantitatively variable.

The author then gives an account of a very extensive investigation into the relatives of 27 patients, the subjects of infantile cerebral palsy and "symptomatic" epilepsy with generalised convulsions; pedigrees of each of the 27 families are given, and information was collected about 1,749 persons. The number of secondary cases of epilepsy discovered was not at all large, but the author also considers the incidence of such possibly related conditions as hemicrania, infantile convulsions, enuresis nocturna, pavor nocturnus, etc. The psychopathic members of these families were predominantly of the excitable, explosive type, this temperament being often combined with an athletic habitus. The relationship with psychoses, psychogenic and hysterical attacks, mental deficiency and such other anomalies as left-handedness is also covered.

Although the results obtained suggest no new conclusions of a revolutionary kind, the contribution which is made to the problem of genetical ætiology is a valuable and a significant one.

ELIOT SLATER.

ANOSOGNOSIA

Denial of Illness. By EDWIN A. WEINSTEIN, M.D., and ROBERT L. KAHN, Ph.D. 1955. Pp. 166. Illinois: Charles C. Thomas. 34s.

This is a stimulating book which should be of interest to the psychiatrist as much as to the neurologist. The authors reject the view that denial of illness in its many forms is exclusively determined by the site of brain damage. Whether a lesion involves the frontal or parietal lobes, for instance, determines not the mechanism of denial but the kind of disability denied. Anosognosia is regarded as something very different from a fixed defect caused by a focal brain lesion. On the contrary, they believe that some at least of these mechanisms, resulting in denial of illness (either verbal or implicit in behaviour) are to be seen in the language and behaviour of everyday life: and that for this reason alone the study of anosognosia is worth while.

All language, they point out, involves processes of selection and generalization. The units of language can be arranged for referential communication, but also in other ways for expressing movitation, as in humour, myth, poetry, and religion: and in these latter symbolic systems such mechanisms as reduplication, paraphasia and disorientation appear as in the brain-diseased. All these modes of language provide a means of adapting to the stresses of existing. Normally there is interplay between these various symbolic systems; but in the brain-diseased this flexibility may be lacking.

In the confabulations of children and the dreams of the adult, symbolic expressions of motivation are to be seen of a kind seen in the brain-diseased who deny illness: and just as the young child does not stop to consider whether his play representations are real or not, so, too, the patient with anosognosia is concerned not with truth or falsehood but only with escape from the intolerable.

Although the site of brain damage may determine what is to be denied, there are many factors which the authors think determine the pattern of denial—the patient's motivation, his particular symbolic values and the individual way in which he organizes his percepts so that they express his motivations.

This book has resulted from the patient study not only of an impressive number of cases showing anosognosia but also of patients who, though not denying their disabilities verbally, yet adapt to their illness by such kindred processes as disorientation, reduplication (for time, place, person and parts of the body), paraphasia, inattention, withdrawal and pain asymbolia.

With the authors' views outlined above this reviewer agrees. In a short book they cover this difficult field in the borderland between neurology and psychiatry with a fair degree of clarity. They never fail to capture the reader's interest.

PAUL SANDIFER.

STATUS DYSRAPHICUS

Status Dysrhaphicus. By LAURENS BIJL. 1956. Pp. 283. Tables 24. Figs. 26. Uitgeverij & Drukkerij Hollandia N.V.– Baarn, Holland.

Since the days of Lombroso and his descriptions of "degenerative types" and "stigmata," ideas have been current in the medical literature, especially of German-speaking countries, concerning the relationship of certain stigmata to heredo-familial disorders of the nervous system. These views culminated in the introduction of the term *"Status Dysraphicus"* by Bremer in 1926. While studying the heredity of syringomyelia he found that patients and relatives frequently possessed a similar type of physical constitution which he subsequently called "status dysraphicus". The term itself derived from his observation that varieties of spina bifida and the myelodysplasia of Fuchs were commonly encountered in his families. Other features were funnel chest, kyphoscoliosis, increased span, acrocyanosis, disturbances of sensibility, anomalies of the teeth, palate and hairgrowth, and finally enuresis. Bremer soon found these constitutional types in families without syringomyelia.

Bijl has conducted a statistical enquiry into the incidence of status

dysraphicus in two groups of Dutch conscripts examined in Utrecht in 1944 and in 1948 (6,368 men). He recorded the frequency and severity of each of the individual "components" of the dysraphic syndrome and studied their mutual correlation. In 1944 15·6 per cent and in 1948 19·3 per cent of the conscripts were classified as belonging to this type of constitutional group. The author has drawn up a standard list of signs and in addition to those already mentioned he has included "gothic" palate, clinodactylism, Horner's syndrome (with or without heterochromia), vertebral anomalies, congenital club feet, flat feet, hollow feet, claw toes and myelodysplasia. Enuresis he considers an important characteristic of status dysraphicus; more than 50 per cent of recruits with enuresis persisting in adult life had a dysraphic anomaly of the spine. He does not conclude that enuresis is directly dependent on the presence of spina bifida or some other type of vertebral anomaly but rather that it is another manifestation of the whole dysraphic constitutional type. That enuresis can be influenced by psychological treatment he does not consider an argument against this view.

A chapter is devoted to an account of coexisting anomalies of the supporting tissues, the cardiovascular and the urogenital systems. There was a greater incidence of defective intelligence and mental instability in the dysraphic group than in the normal group.

Little is known of the heredity of status dysraphicus. The author stresses the incompleteness and the small scale of the published hereditary studies. One cannot decide solely from the nature of the anomaly whether it is hereditary or acquired. Experimental embryological studies have shown that during the first period of embryonic life the internal condition of the cytoplasm influences the growth of the embryo more than do genetic factors. The patterns of anomalies due to dysontogenetic disturbance of the dorsal lip of the blastopore may be very similar whether the influences are genetic or environmental.

The author discusses the literature and critically examines the works of Bremer, Curtius and Sillevis Smitt under whose ægis the investigation was conducted. He seems to have clarified the position of status dysraphicus, and has separated out the harmless anatomical variants from the "stigmata of degeneration". To this reviewer much of the literature on the subject of dysraphism has had an air about it of "Beware of the man whose eyebrows meet."

It is not a very readable monograph and the author's English sometimes makes it difficult to follow his reasoning. There is an adequate summary, 142 references, but no index.

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LEUCOTOMY

Personality Changes Following Frontal Leucotomy. By P. MACDONALD TOW. 1955. Pp. 262. Illus. 6. London: Oxford University Press. 35s.

This is an extremely well-written book; in fact, Part I is as good a summary of our knowledge of the frontal lobe as any that I have read.

The value of Dr. Tow's work as a piece of neuro-psychiatric research is,

however, more difficult to assess. It is unfortunately true that delays in publication make many accounts of original research work already out of date by the time that they appear—in other words, there is nearly always a time-lag in that sense—but it is very difficult to determine which of Dr. Tow's cases belong to his 1947 series and which are more up to date.

It would be agreed, I think, that the standard leucotomy operations performed on the 36 patients with neurotic or psychopathic personality-disorders, which form the case-material for the study, would nowadays be considered unsuitable. For there is enough evidence to suggest that modified operations can bring about as good clinical results in many of these cases without causing the same disquieting personality-distortions in persons with pre-existent personality-defects.

These changes, as summarized by the author, are quoted by Sir Russell Brain in his foreword to the book: "there seems to be impairment of the powers of abstraction and synthesis; of perception of relations and differences; of the ability to deal with complex situations, planning, and the thinking out of the next action and its consequences; and appreciation of one's own mistakes. . . . There is also impairment of the power of sustained attention and of the capacity for fine discrimination; and a dulled appreciation of the subject's own level of success or failure."

These observations amply confirm those of other observers in this field and should influence neuro-psychiatrists to be prudent and cautious before recommending cerebral surgery for purely psychiatric purposes.

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